REACTIONS OF
ORGANIC COMPOUNDS

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REACTIONS OF ORGANIC COMPOUNDS

BY

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PREFACE

NOTWITHSTANDING the numerous books on Organic Chemistry which are from time to time appearing, the author feels that there is still room for a volume which approaches the subject from a somewhat different standpoint. Instead of following the normal course, he has endeavoured to present a comprehensive account of the reactions of typical groups essentially from the point of view of laboratory practice. He has also endeavoured, wherever possible, to indicate the limitations of the so-called "general reactions." As a logical development of the treatment herein adopted, an appendix has been included on the identification of Organic Compounds.

In conclusion, the author acknowledges with pleasure the assistance which he has received from the Rev. Dr. A. J. Cooper, F.I.C., formerly headmaster of Solihull School, who has read the whole of the manuscript and helped with many useful suggestions.

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TABLE OF ABBREVIATIONS USED IN THE REFERENCES

Abbreviated Title.	Full Title.
A.	Abstracts in Journal of Chemical Society, or, after 1925, British Chemical Abstracts, Section A.
Amer. Chem. J.	American Chemical Journal.
Annalen	J. Liebig's Annalen der Chemie.
Annalen Spl.	J. Liebig's Annalen der Chemie. Supplementband.
Ann. Chim.	Annales de Chimie.
Ann. Farm. Chim.	Annali di Farmacoterapia et Chimica.
Ann Rpts.	Annual Reports of the Chemical Society.
Atti R. Accad. Lincei	Atti della Reale Accademia Nazionale dei Lincei.
B.A. Report	Reports of the British Association for the Advancement of Science.
Ber.	Berichte der deutschen chemischen Gesellschaft.
Ber. deut. pharm. Ges.	Berichte der deutschen pharmazeutischen Gesellschaft.
Biochem. J.	Biochemical Journal.
Bull. Acad. roy. Belg.	Bulletin de la Classe des Sciences, Académie royale de Belgique.
Bull. Soc. chim.	Bulletin de la Société chimique de France.
Bull. Soc. chim. Belg.	Bulletin de la Société chimique de Belgique.
Chem. News	Chemical News.
Chem. Zeit.	Chemiker-Zeitung.
Coll. Czech. Chem. Comm.	Collection of Czechoslovak Chemical Communications.
Compt. rend.	Comptes rendus hebdomadaires des Séances de l'Académie des Sciences.
D.R.-P.	Deutsches Reichs-patent.
E.P.	English Patent.
F.P.	French Patent.
Gazzetta	Gazzetta chimica italiana.
Helv. Chim. Acta	Helvetica Chimica Acta.
J.	Transactions of the Chemical Society, Journal of the Chemical Society.
J. Amer. Chem. Soc.	Journal of the American Chemical Society.
J. Ind. Chem. Soc.	Quarterly Journal of the Indian Chemical Society.
J. Ind. Eng. Chem.	Journal of Industrial and Engineering Chemistry.
J. Ind. Inst. Sci.	Journal of Indian Institute of Science.
J. Pharm. Chim.	Journal de Pharmacie et de Chimie.

ABBREVIATIONS USED IN THE REFERENCES

Abbreviated Title.	Full Title.
J. pr. Chem.	Journal für praktische Chemie.
J. Roy. Tech. College Glasgow	Journal of the Royal Technical College, Glasgow.
J. Russ. Phys. Chem. Soc.	Journal of the Physical and Chemical Society of Russia.
J.S.C.I.	Journal of the Society of Chemical Industry.
Monatsh.	Monatshefte für Chemie.
Nature	Nature.
Perf. and Essential Oil Record	Perfumery and Essential Oil Record.
Phil. Trans.	Philosophical Transactions of the Royal Society of London.
Proc. K. Akad. Wetensch. Amsterdam	Koninklijke Akademie van Wetenschappen te Amsterdam.
Proc. Roy. Dub. Soc.	Scientific Proceedings of the Royal Dublin Society.
Proc. Roy. Irish Acad.	Proceedings of the Royal Irish Academy.
Proc. Roy. Soc.	Proceedings of the Royal Society of London.
Rend. Accad. Sci. Fis. Mat. Napoli	Rendiconto dell' Accademia delle Scienze Fisiche e Matematiche, Napoli.
Rec. trav. chim.	Recueil des travaux chimiques des Pays-Bas et de la Belgique.
Svensk Kem. Tidsk.	Svensk Kemisk Tidskrift.
Z.	Chemisches Zentralblatt.
Z. angew. Chem.	Zeitschrift für angewandte Chemie.
Z. phys. Chem.	Zeitschrift für physikalische Chemie.
Z. physiol. Chem.	Hoppe-Seyler's Zeitschrift für physiologische Chemie.

Other Abbreviations.

alc.	Alcohol or alcoholic (according to context).
aq.	Aqueous.
b.p.	Boiling point.
d.	Density. The temperature at which the density is determined and the temperature of water used as standard are placed after the value of the density. Thus $0{\cdot}823^{20}_{4}$.
dec.	Decomposition.
m.p.	Melting point.
sol.	Solution or soluble or solubility according to the context.
[ ]	This denotes in a column headed B. p. that the substance is solid. The figures enclosed in the brackets give the m. p. In a column headed M. p. this denotes that the substance is liquid, and the figures give the b. p.

The abbreviations Me, Et, Pr, Bu, Ph, etc., have been employed in formulæ and in the text for Methyl, Ethyl, Propyl, Butyl, Phenyl, etc.

(I) PARAFFINS, *cyclo*HEXANE, OLEFINS, AND ACETYLENES

(1)a. Paraffins.
(1)b. *cyclo*Hexane.
(2). Olefins.
  1. Addition of Hydrogen.
  2. Addition of the Elements of Water.
  3. Addition of Oxygen and Hydroxyl.
    (*a*) Formation of Glycols and Ethylene Oxides.
    (*b*) Formation of Ozonides.
  4. Addition of Halogen.
  5. Addition of Halogen Hydrides.
  6. Addition of Hypochlorous, Hypobromous, and Hypoiodous Acids.
  7. Addition of Nitrosyl Chloride and Oxides of Nitrogen.
  8. Other Additive Reactions.
  9. The Influence of Structure and other Factors on Additive Reactions.
  10. Isomerisation of Unsaturated Compounds.
(3) Acetylenes.

(1)a. *Paraffin Hydrocarbons.*

THE saturated open-chain hydrocarbons are distinguished from unsaturated and aromatic hydrocarbons by their inertness towards cold concentrated or fuming sulphuric acid. It is thus possible to separate the constituents of a mixture of paraffins and aromatic hydrocarbons by shaking it with cold fuming sulphuric acid (15%), the paraffins remaining undissolved. Sulphuric acid forms a separate layer containing the sulphonic acids of the aromatic hydrocarbons. The undissolved hydrocarbons should be submitted to a further treatment with fuming sulphuric acid and then washed with alkali and water.

The prolonged action of hot concentrated sulphuric acid on the paraffins leads to substitution. The *normal* paraffins appear to be the most resistant, for, even after very lengthy treatment, the amount of sulphonic acid formed is comparatively small; hydrocarbons with branched chains are attacked more readily. This appears to be a general rule, for paraffins with branched chains react more readily with chlorosulphonic acid than the *normal* hydrocarbons (Young, *J.*, 1899, **75**, 172). Hydrocarbons with unbranched chains are also less reactive towards concentrated nitric acid than the *iso-* and *tertiary* paraffins. Thus the *normal* paraffins are unacted upon at room temperature; even after a prolonged heating at 100° the greater part of the paraffin can be recovered unchanged (Francis and

Young, *J.*, 1898, **73**, 928; Markovnikoff, *Ber.*, 1899, **32**, 1441; *J. pr. Chem.*, 1899, [ii], **59**, 556; compare Worstall, *Amer. Chem. J.*, 1898, **20**, 202, 665; 1899, **21**, 219). *Tertiary* paraffins, however, are oxidised comparatively readily by fuming nitric acid yielding fatty acids, carbon dioxide, and small amounts of nitro-compounds. *iso*Paraffins—of not too low boiling point—are partly oxidised and partly nitrated by heating under reflux with fuming nitric acid (Markovnikoff, *loc. cit.*; Francis and Young, *loc. cit.*; Konovaloff, *J. Russ. Phys. Chem. Soc.*, 1906, [i], **38**, 109, 124).

The introduction of nitro-groups into paraffins is best effected by heating in sealed tubes with dilute nitric acid (*d* 1·07—1·15) at 110—120°. For details see Konovaloff (*loc. cit.*).

The *normal* paraffins are not easily oxidised and are indifferent to cold neutral, alkaline, or acid permanganate and to cold chromic acid. Even on heating, the oxidation proceeds but slowly and with difficulty. Recently, a considerable amount of attention has been directed to the oxidation of paraffins by air, oxygen, or nitrous fumes. Thus, Wood and Francis (*J.*, 1927, 1897) found that triacontane oxidised at 95° by a stream of air during 400 hours gave a mixture of unchanged hydrocarbon, fatty acids, secondary alcohols, and ketones. The acids were present largely as esters and amounted approximately to 65% of the product. For descriptions of the products and the experimental conditions for oxidation of paraffin wax see Francis (*J.*, 1922, 496), Francis and Gauntlett (*ibid.*, 1926, 2377), Franck (*Chem. Zeit.*, 1920, **44**, 309), M. Bergmann (*Z. angew. Chem.*, 1918, **31**, 69), Kelber (*Ber.*, 1920, **53**, 66), Grün and Ulbrich (*Z. angew. Chem.*, 1923, **36**, 125), Gränacher (*Helv. Chim. Acta*, 1920, **3**, 721), Gränacher and Schaufelberger (*ibid.*, 1922, **5**, 392).

Bromine and chlorine react very slowly with the paraffins to form substitution products, but the reaction can be accelerated by the addition of halogen carriers such as iodine, antimony chloride, iron powder, or aluminium. The rate of substitution is also favoured by exposure to sunlight.

√ (1)b. cyclo*Hexane and its Homologues.*

These hydrocarbons, containing a saturated ring of six carbon atoms, resemble the paraffins in their indifference to cold nitric and sulphuric acids. By warming with fuming nitric acid on a water-bath for several hours, *cyclo*hexane is oxidised with the formation of a mixture of glutaric and adipic acids; a small amount of succinic acid and nitro-compounds is also produced (Markovnikoff, *Annalen*, 1898, **302**, 7). The nitration of *cyclo*hexane can be achieved by heating the hydrocarbon in a sealed tube with dilute nitric acid (*d* 1·075—1·2) at temperatures of 105—115°, but it appears that even under these conditions small amounts of adipic acid are formed (Markovnikoff, *loc. cit.*; Nametkin, *J. Russ. Phys. Chem. Soc.*, 1908, **40**, 1570; 1909, **41**, 145).

Fuming sulphuric acid (15—20%) has little action on *cyclo*hexane at room temperature if the contact is not unduly prolonged. The aromatic hydrocarbons under these conditions readily form sulphonic acids; consequently *cyclo*hexane and its homologues can be freed from associated aromatic hydrocarbons by treatment with 15% oleum. Prolonged contact with the acid must be avoided in such a separation, otherwise dehydrogenation of the *cyclo*hexane may occur with the formation of an aromatic hydrocarbon and subsequent formation of a sulphonic acid. Thus, Menschutkin and Wolff (*Coll. Czech. Chem. Comm.*, 1930, **2**, 396) found that by shaking *cyclo*hexane at 25° repeatedly with fresh portions of 25% oleum, the *cyclo*hexane was gradually converted into benzenesulphonic acid with the simultaneous formation of sulphur dioxide and some tar. H. Meyer (*Annalen*, 1923, **433**, 350) also records that methyl*cyclo*hexane can be converted into *p*-toluenesulphonic acid by the prolonged action of concentrated sulphuric acid at 100°. In this connection it is interesting to note that the dehydrogenating action of warm concentrated sulphuric acid was employed by Baeyer (*Annalen*, 1873, **166**, 325; *Annalen Spl.*, 1870, **7**, 23) to convert hexahydromellitic acid into tri- and tetra-carboxylic derivatives of benzene.

Dehydrogenation of cyclo*Hexane.*

A number of methods have been described for converting *cyclo*hexane and its derivatives into aromatic compounds. The action of an excess of bromine and some aluminium bromide or chloride at room temperature on homologues of *cyclo*hexane results in simultaneous dehydrogenation and bromination with the formation of tri- and tetra-brominated aromatic hydrocarbons. By this method identification of the polymethyl*cyclo*hexanes without ambiguity is possible, the alkyl groups being undisturbed during the reaction (Konovaloff, *J. Russ. Phys. Chem. Soc.*, 1887, **1**, 255; Markovnikoff, *Compt. rend.*, 1892, **115**, 440). A process, which allows the estimation of *cyclo*hexane in presence of paraffin hydrocarbons, consists in the catalytic dehydrogenation by passing vaporised hydrocarbons over finely-divided platinum or palladium kept at about 300° (Tausz and Putnoky, *Ber.*, 1919, **52**, 1575; compare Zelinski, *ibid.*, 1912, **45**, 3678; 1923, **56**, 787, 1718; Zelinski and Pavloff, *ibid.*, p. 1249). Recently selenium and sulphur have been used with considerable success for dehydrogenation of reduced aromatic hydrocarbons, in particular di- and tri-cyclic compounds (Ruzicka and J. Meyer, *Helv. Chim. Acta*, 1921, **4**, 505; 1922, **5**, 581; Ruzicka, Meyer, and Mingazzini, *ibid.*, 1922, **5**, 345; Diels, Gädke, and Körding, *Annalen*, 1927, **459**, 1; Harvey, Heilbron, and Wilkinson, *J.*, 1930, 423; Heilbron and Wilkinson, *ibid.*, p. 2537).

(2) *Olefins.*

In contrast to the saturated hydrocarbons, which are comparatively stable and show no tendency towards the formation of additive compounds, hydrocarbons containing double bonds are reactive, forming additive compounds with a variety of reagents and being sensitive to oxidation. It is therefore comparatively easy, under all normal conditions, to detect the presence of unsaturation. Thus, while paraffins and aromatic hydrocarbons are not affected by cold aqueous permanganate, the olefins are oxidised with the discharge of the colour of the permanganate and the production of brown manganese dioxide. This test is due to Baeyer (*Annalen*, 1888, **245**, 146), and, taken in conjunction with other reactions, enables a distinction to be made between olefins and saturated compounds. This test can also be applied to detect the presence of unsaturation in acids; >CH·OH or —CHO groups are usually attacked slowly by cold neutral permanganate, so that the presence of double bonds in aldehydes and alcohols is indicated by the rapidity with which the permanganate is decolorised.

Other reagents have been suggested for the detection of unsaturation. Baeyer and Villiger (*Ber.*, 1900, **33**, 2496) have proposed the use of a solution of potassium persulphate in sulphuric acid tinted with permanganate. This reagent gives no reaction with pure paraffin hydrocarbons, but attacks olefins and benzene and its homologues. It is also stated to oxidise *cyclo*hexane slowly.

Tetranitromethane has also been proposed as a reagent for the double bond, as it gives a brown or yellow coloration with unsaturated compounds (A. Werner, *Ber.*, 1909, **42**, 4324). It is, however, extremely sensitive, and most specimens of paraffin hydrocarbons give colorations, owing to the presence of traces of impurities. These last two tests would appear to be more suited to the detection of small amounts of unsaturated compounds in paraffin hydrocarbons.

The principal reaction of unsaturated linkages is the ability to combine additively with a large variety of substances resulting in the formation of saturated compounds.

1. *Addition of Hydrogen.*

The combination of a double bond with hydrogen can be achieved by one of the catalytic methods involving the use of molecular hydrogen or by the action of a suitable reducing agent such as sodium and alcohol, or acid and a metal, or hydriodic acid and amorphous phosphorus.

The catalytic method of hydrogenation may be considered, as far as technique is concerned, as of two distinct types: (*a*) hydrogenation in the gaseous phase and (*b*) hydrogenation in the liquid phase.

(*a*) By the former method, the vaporised substance to be reduced is mixed with hydrogen and led over finely-divided nickel or some other catalyst maintained at the appropriate temperature. This type of reduction was introduced by Sabatier and Senderens (*Compt. rend.*, 1899, **128**, 1173; 1900, **130**, 1761; 1901, **132**, 210, 566, 1254; 1902, **134**, 1127; 1902, **135**, 87), and very largely developed by them. Nickel supported on pumice is the catalyst usually applied for the reduction of unsaturated compounds, but other porous materials, such as pieces of unglazed earthenware, charcoal, fuller's earth, have been used as supports with good effect. The catalyst is prepared by impregnating the support with nickel oxide and then reducing.

Preparation of the Catalyst.—Small pieces of pumice, purified by boiling with concentrated nitric acid and then washing with water, are stirred with a concentrated solution of nickel nitrate, and the mixture is evaporated to dryness in a porcelain dish with constant stirring to ensure an even mixture. The amount of nickel nitrate taken should be such that the catalyst will contain approximately 20—40% of nickel.

The dried mixture is transferred to a nickel dish and heated over a free flame until the nitrate is completely decomposed. The mass is then introduced into a hard glass combustion tube, freed from air by a vigorous current of hydrogen, and then heated at about 300–400° in a stream of hydrogen till reduction of the oxide to metal is complete. It is then cooled in hydrogen and is used directly for reduction.

Preparation II.—Hydrated nickel nitrate (75 g.) is dissolved in water and a paste made by adding about 60 g. of carefully purified kieselguhr. (The guhr is purified by boiling with concentrated nitric acid, and then several times with water, subsequently filtering and draining.) To the paste an excess of sodium carbonate solution is added and the mixture boiled for a short time. After settling, the supernatant solution is decanted off and the residue washed several times with hot water till free from alkali. It is then drained on a funnel and dried in a porcelain dish on a steam bath. The powder so obtained is introduced into a hard glass combustion tube and reduced to the metal in the manner previously described.

A similar process can be employed for the production of finely-divided nickel on other supports such as pumice, animal charcoal, etc.

The reduction is effected by passing the vaporised substance mixed with hydrogen over the catalyst maintained at a suitable temperature. If the substance is a gas, it is only necessary to mix it with an excess of hydrogen before leading it into the tube. With liquids it is usual to pass hydrogen through the substance maintained at a temperature sufficiently below its boiling point that it vaporises readily without boiling.

After leaving the tube, the product is collected by cooling with water or air. If volatile, special apparatus cooled in ice and salt, solid carbon dioxide and ether, or even liquid air may be required.

The temperature of reduction is dependent on the nature of the substance, ethylene and its homologues being reduced at 120—150°; aromatic hydrocarbons require a temperature of about 200°. The method has also been used for the reduction of unsaturated ketones and aldehydes, as well as for the reduction of aldehydes and ketones to the corresponding alcohols, and of nitro-compounds to amines.

(*b*) The catalytic reduction of unsaturated compounds can also be effected in the liquid state by hydrogen in presence of a catalyst. Finely-divided nickel has been extensively used in this way for the technical hydrogenation of unsaturated fats and oils. The method can also be used on a laboratory scale for the reduction of olefins, unsaturated acids, alcohols, azomethines, etc. The most generally applied processes are, however, those using colloidal platinum or palladium as catalyst.

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The laboratory apparatus used for catalytic reduction consists essentially of a container for the hydrogen, and a hydrogenation flask, which can be shaken mechanically. The unsaturated substance and a suitable preparation of the catalyst are introduced into the hydrogenation flask and shaken in an atmosphere of hydrogen. It is usual to have some device for measuring the volume of hydrogen, so that the progress of the hydrogenation can be followed. Many forms of apparatus have been described, and the original papers should be consulted for the details (Paal and Gerum, *Ber.*, 1908, **41**, 813; Willstätter and Hatt, *ibid.*, 1912, **45**, 1472; Skita and W. A. Meyer, *ibid.*, 1912, **45**, 3594; Stark, *ibid.*, 1913, **46**, 2335; Rosenmund and Zetsche, *ibid.*, 1918, **51**, 580; Adams and Voorhees, *J. Amer. Chem. Soc.*, 1922, **44**, 1403; *Organic Syntheses*, 1928, **8**, 10).

For the quantitative determination of unsaturation, on a small scale, the following process has been found to be effective. The absorption vessel used is represented diagrammatically in Fig. 1. It is clipped on a light metal carriage, which is shaken mechanically. The tube *A* is attached by means of reasonably light rubber pressure tubing (covered with insulating tape) to a gas burette of 100 c.c. or some other suitable capacity. It is advantageous to insert a plug of cotton wool in *A* to prevent fragments of rubber entering the absorption vessel.

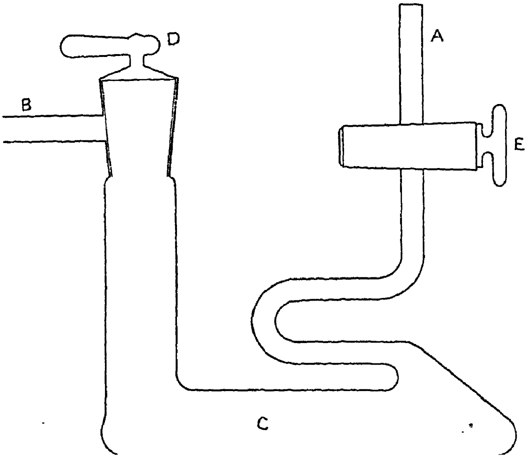


FIG. 1.
(About half size.)

The greater part of the solvent—acetic acid, ethyl alcohol, or ethyl acetate—is introduced with the catalyst through the tap *D*. The tap *D* is then replaced and turned so that a rapid stream of hydrogen from a cylinder may be passed through the apparatus through the tube *B*. During the flushing of the apparatus, the tap *E* is kept open in order to remove all traces of air from the rubber connections and the gas burette taps.

When the system is free from air, hydrogen is introduced into the gas burette, the tap *D* closed, and the vessel shaken till all absorption of hydrogen is complete. At this stage a weighed amount of the substance to be hydrogenated dissolved in the remainder of the solvent is introduced through *D*, the apparatus flushed out with hydrogen, and the gas burette filled. After closing tap *D*, the vessel is shaken until no more absorption occurs.

This method gives good results with substances which are hydrogenated rapidly. When the rate of absorption is slow, an appreciable error is introduced by the slow diffusion of hydrogen through the rubber connections.

A number of processes of catalytic reduction have been described which differ essentially only in the preparation of the catalyst. Paal and his co-workers have used colloidal suspensions of platinum or palladium protected by the colloidal products of the alkaline hydrolysis of egg albumin (Paal and Gerum, *Ber.*, 1908, **41**, 2273; 1909, **42**, 1553; Paal and Roth, *ibid.*, 1908, **41**, 2282; 1909, **42**, 1541; Paal and Hartmann, *ibid.*, 1909, **42**, 2239, 3930; 1910, **43**, 243). Gaseous hydrogen and such a catalyst reduce olefinic and acetylenic acids, unsaturated hydrocarbons, ketones, and aldehydes to the corresponding saturated compounds. The method does not appear to be suitable for the hydrogenation of the aromatic nucleus, nor does it appear to reduce the carbonyl group. The protective colloid of the catalyst is sensitive to acids, consequently the method can only be applied in neutral or alkaline solution.

The use of colloidal platinum or palladium protected by gum arabic has been developed by Skita and his co-workers (Skita, *Ber.*, 1909, **42**, 1627; Skita and Ritter, *ibid.*, 1910, **43**, 3393; Skita and H. H. Franck, *ibid.*, 1911, **44**, 2862; Skita, *ibid.*, 1912, **45**, 3312; 1915, **48**, 1486; Skita and W. A. Meyer, *ibid.*, 1912, **45**, 3579, 3589; Skita and W. Brunner, *ibid.*, 1916, **49**, 1597). In its simplest form this method consists in adding a small quantity of palladous chloride solution acidified with hydrochloric acid to an aqueous solution or aqueous alcoholic solution of the unsaturated substance, and then shaking the solution in an atmosphere of hydrogen under an excess pressure of about one atmosphere. More generally, the palladous chloride solution containing a small amount of gum arabic is added to the unsaturated substance dissolved in aqueous alcohol or acetic acid. The hydrogenation is then effected in the usual way. These processes are sometimes unsatisfactory owing to the failure of the metal to separate in a colloidal form during the reduction. In these circumstances a trace of preformed colloidal palladium is added before starting the reduction.

Unsaturated acids are reduced to saturated compounds, while aromatic amines and phenols are converted into the corresponding *cyclo*hexane derivatives; carbonyl compounds can be reduced to the corresponding alcohols under suitable conditions. The extent of the hydrogenation is, in some measure at least, influenced by the solvent, the pressure of hydrogen, and the temperature (see Skita, *Annalen*, 1921, **427**, 255; 1923, **431**, 5; *Ber.*, 1923, **56**, 1014, 2234; 1920, **53**, 1803; Skita and Rolfes, *Ber.*, 1920, **53**, 1244; Skita and Schneck, *ibid.*, 1922, **55**, 145).

Willstätter and his co-workers have used colloidal platinum and palladium as catalysts. Their process is well suited for the reduction of aromatic compounds to derivatives of *cyclo*hexane. It differs from the methods of Skita and Paal in that the catalyst has no protective colloid. Certain precautions must be observed in the preparation of the catalyst, and it has been found that the efficiency of the hydrogenation is dependent on the presence of oxygen in the colloidal platinum or palladium.

Preparation of Platinum-black for Hydrogenation by the Willstätter–Fokin Method.—80 C.c. of a solution of chloroplatinic acid (from 20 g. of platinum) containing some hydrochloric acid are mixed with 130 c.c. of formalin solution. After cooling to – 10°, 420 g. of 50% potassium hydroxide solution are added drop by drop, the temperature being kept below 5°. The mixture is stirred continuously during the addition of the alkali. When all has been added, the liquid is heated for ½ hour to 55—60°, the stirring being continued. The platinum-black settles and is washed by decantation in a tall cylinder till there is no reaction for chloridion or alkali. The black is then drained lightly on a funnel, taking care that the platinum is always covered with water. It is finally pressed quickly between filter paper and dried in a vacuum desiccator. Before opening the desiccator, it should be filled with carbon dioxide to prevent the efficiency of the catalyst being impaired.

When the catalyst becomes inactive during use, it can be revived by evacuating the hydrogenation flask and then admitting air and shaking.

Details of the preparation of palladium-black in a form suitable for catalytic reduction of aromatic compounds are given by Willstätter and Waldschmidt-Leitz (*Ber.*, 1921, **54**, 123).

A further modification is due to Adams and his co-workers, who use platinum-black produced by the reduction of platinic oxide, PtO_2,H_2O. In general, the platinic oxide is added to an alcoholic solution of the substance to be reduced, and the hydrogenation is then carried out under two or three atmospheres pressure. Less rarely, glacial acetic acid or ethyl acetate may be used as solvent. A complete account of the preparation of the catalyst is given by Adams, Voorhees, and Shriner (*Organic Syntheses*, 1922, **8**, 92), as well as references to the original papers.

In general, catalytic hydrogenation of the double bond is the most convenient method of reduction. Other methods of reduction include the use of sodium or its amalgam in presence of ethyl or amyl alcohols or of moist ether; aluminium amalgam acting in a moist ethereal solution of the unsaturated substance; less rarely concentrated hydriodic acid and red phosphorus.

Reduction with sodium and alcohol has been employed very frequently, particularly for the reduction of aryl-substituted αβ-unsaturated fatty acids. Purely aliphatic αβ-unsaturated acids are not reduced rapidly by this process; βγ- and γδ-acids are even more resistant (Tollens and Caspary, *Annalen*, 1873, **167**, 255; Fittig and Barringer, *ibid.*, 1872, **161**, 309; Thiele and Meisenheimer, *ibid.*, 1899, **306**, 259).

Preparation of β-Phenylpropionic Acid from Cinnamic Acid.—A mixture of 10 g. of cinnamic acid and 100 c.c. of water is stirred mechanically in a thick-walled beaker. A slight excess of dilute alkali is added and then 2½% sodium amalgam in small pieces is added gradually till about 200 g. have been used. When the reduction is complete, the solution is decanted from the mercury and acidified with hydrochloric acid. β-Phenylpropionic acid is precipitated as an oil, which solidifies on cooling. It is purified by crystallisation from warm water. M.p. 46—47°, yield about 7—9 g.

The use of sodium and alcohol has been applied successfully to the reduction of styrenes and similar substituted ethylenes. It fails apparently with styrenes of the general formula, $Ph{\cdot}CH{:}CR_2$ (Klages, *Ber.*, 1902, **35**, 2646; 1904, **37**, 924, 1721).

The position of the double bond also appears to have an important effect on the ease of reduction. Thus, while safrol and apiol are scarcely attacked, their isomers, *iso*safrol and *iso*apiol, are smoothly reduced (Ciamician and Silber, *Ber.*, 1890, **23**, 1162, 2285; compare Klages, *ibid.*, 1899, **32**, 1436).

The following papers may be consulted for accounts of the use of aluminium amalgam in the reduction of unsaturated compounds in moist ethereal solution : Thiele and co-workers, *Annalen*, 1906, **347**, 260, 279, 293 ; Henle, *ibid.*, 1906, **348**, 16 ; Sieglitz and Jassoy, *Ber.*, 1921, **54**, 2135.

2. *Addition of the Elements of Water.*

The simple olefins appear to be unacted on by pure water—ethylene can be heated with water to 200° at a pressure of about 100 atmospheres without any reaction taking place. They combine additively with sulphuric acid to give alkyl hydrogen sulphate, from which the alcohol can be obtained by simple hydrolysis :—

$$CH_2{:}CH_2 + H_2SO_4 \longrightarrow CH_3{\cdot}CH_2{\cdot}O{\cdot}SO_3H \xrightarrow{H_2O} CH_3{\cdot}CH_2{\cdot}OH + H_2SO_4$$

This reaction appears to have been first observed by Hennel (*Phil. Trans.*, 1826, 248; compare Faraday, *ibid.*, 1825, 448). He found that after absorbing ethylene in sulphuric acid, ethyl alcohol was obtained by diluting the solution and distilling. The homologues behave similarly, although with the higher members there is an increasing tendency to polymerise (Butleroff, *Annalen*, 1877, **189**, 44; King, *J.*, 1919, **115**, 1407; Brooks and Humphrey, *J. Amer. Chem. Soc.*, 1918, **40**, 822). Solution of the olefin in sulphuric acid of suitable concentration and subsequent hydrolysis is a convenient method of converting olefins into alcohols ; the addition with simple olefins occurs so that the hydroxyl group is attached to the carbon atom carrying the fewest hydrogens, as the following examples indicate :—

$$Me{\cdot}CH{:}CH_2 \longrightarrow Me{\cdot}CH(OH){\cdot}CH_3,\quad Me_2C{:}CH_2 \longrightarrow Me_2C(OH){\cdot}CH_3,$$
$$Et{\cdot}CH{:}CH_2 \longrightarrow Et{\cdot}CH(OH){\cdot}CH_3$$

The rate of reaction of the unsaturated compound with sulphuric acid appears to be determined by the nature of the groups adjacent to the double bond. An accumulation of negative groups has the effect of retarding the addition. Dichloroethylene, cinnamic acid, and fumaric acid are comparatively inert to sulphuric acid. The lower olefins show considerable differences in the ease with which they react with sulphuric acid. Ethylene combines rapidly with sulphuric acid at 70° to give a solution containing ethyl hydrogen sulphate (Plant and Sidgwick, *J. Soc. Chem. Ind.*, 1921, **40**, 14T). The butylenes and higher homologues dissolve readily in concentrated sulphuric acid at room temperature, but undergo extensive polymerisation. With diluted sulphuric acid they react, giving the alcohol and alkyl hydrogen sulphate. A wide choice of acid concentration between 60 and 80% can be employed, according to the olefin under treatment. Thus, *iso*butylene, $(CH_3)_2C{:}CH_2$, is rapidly absorbed by 63% sulphuric acid (Michael and Brunel, *Amer. Chem. J.*, 1909, **41**, 118), while the other isomers are not appreciably affected by this concentration of acid. They dissolve, however, in 80% acid, giving the corresponding butyl hydrogen sulphates. The rate of reaction of the olefins with diluted sulphuric acid has been found to be in the following order :—

$$Me_2C{:}CH_2 > MeCH{:}CHMe > EtCH{:}CH_2$$
$$Me_2C{:}CH_2 > Me_2C{:}CHMe > Me_2C{:}CMe_2$$

According to Brooks and Humphrey (*loc. cit.*), the tendency to yield alcohols and alkyl hydrogen sulphates reaches a maximum with amylene and the hexenes, higher members of the series showing an increasing tendency to polymerise.

Preparation of tert.*-Butyl Alcohol from* iso*Butylene.*—The *iso*butylene is prepared by the dehydration of *iso*butyl alcohol by passing it over alumina deposited on pumice at 500—520°. It is condensed in bottles containing kerosene cooled to — 15° (see p. 91). The solution of butylene is mixed with a cooled 50% solution of sulphuric acid and the mixture stirred for several hours, the temperature being allowed gradually to reach that of the room. The aqueous solution is separated, and dropped slowly into well-cooled dilute alkali. Steam distillation of the product gives a distillate containing *tert.*-butyl alcohol. The alcohol is separated from the bulk of the water by the addition of potassium carbonate, dried over anhydrous potassium carbonate and distilled (Read and Prisley, *J. Amer. Chem. Soc.*, 1924, **46**, 1512).

Preparation of sec.*-Butyl Alcohol from* Δ^β*-Butylene.*—Δ^β-Butylene is prepared by the catalytic dehydrogenation of *n*-butyl alcohol by means of phosphorus pentoxide. It is then cooled by passage through a coil surrounded by ice and salt. The end of the coil dips into a bottle containing 75% sulphuric acid and similarly cooled. The bottle is weighed at intervals, and when the increase in weight corresponds approximately to 10% in excess of the theoretical requirement (calculated from the weight of sulphuric acid taken), it is closed by a rubber stopper, which must be wired down, and shaken for several hours. The product is then diluted and distilled in steam. The alcohol is recovered from the distillate by the addition of potassium carbonate, dried over the same reagent, and fractionated. The yield of *sec.*-butyl alcohol, b. p. 98—100°, is approximately 90% of theory (King, *J.*, 1919, **115**, 1407).

Benzenesulphonic acid may be used instead of sulphuric acid for the conversion of olefins into alcohols (Brooks and Humphrey, *loc.*

cit.). For the use of a mixture of benzenesulphonic acid and acetic anhydride for the hydration of terpenes see Barbier and Grignard (*Bull. Soc. chim.*, 1909, [iv], 5, 512).

Organic acids as formic, acetic, propionic, or butyric have been found to combine with *iso*butylene and trimethylethylene under the influence of zinc chloride to give esters of *tert.*-butyl and *tert.*-amyl alcohols (Kondakoff, *J. pr. Chem.*, 1894, [ii], **48**, 479). For the application of this reaction to the terpene series see Bertram and Walbaum (*ibid.*, 1894, [ii], **49**, 1).

3. *Addition of Oxygen and Hydroxyl.*

(a) *Formation of Glycols and Ethylene Oxides.*—The oxidation of ethylenic compounds by cold neutral aqueous permanganate gives a glycol as the first product :—

$$>C{:}C< + H_2O + O \longrightarrow >C(OH){\cdot}C(OH)<$$

This type of oxidation has been employed extensively with unsaturated hydrocarbons and alcohols. The general method is to add gradually a cold dilute solution of permanganate, corresponding to somewhat more than one atomic proportion of available oxygen, to the unsaturated compound. If the substance is insoluble in water, it is brought into reaction by vigorous stirring, or more efficiently by using acetone as a solvent. When the oxidation is complete, the precipitate of hydrated manganese dioxide is collected, and the filtrate concentrated after neutralising with dilute sulphuric acid or by saturating with carbon dioxide. If the glycol does not separate from the concentrated residue, it is isolated by extraction with alcohol or ethyl acetate (Wagner, *Ber.*, 1888, **21**, 1230, 3347; 1890, **23**, 2313; 1894, **27**, 1644).

*Oxidation of Allyl-*p*-nitrobenzoate to Glycerol α-*p*-Nitrobenzoate.*—A solution of 0·5 g. of allyl-*p*-nitrobenzoate in 100 c.c. of acetone is treated with 79 c.c. of 1% aqueous permanganate. After some hours the manganese dioxide is removed by filtration and the filtrate neutralised with dilute hydrochloric acid. The acetone is distilled off, and the residue concentrated to 40—50 c.c. on the water-bath. The hot filtered solution is kept overnight, when 0·25 g. of pure crystalline glycerol α-mono-*p*-nitrobenzoate separates, m. p. 107° (Fairbourne and Foster, *J.*, 1926, 3147).

Oxidation of Cinnamic Acid to Phenylglyceric Acid.—The cinnamic acid is converted first into the methyl ester by reaction with methyl sulphate. 20 G. of cinnamic acid in 130 c.c. of water are neutralised by the addition of solid potassium hydroxide, the solution being warmed. After cooling, 40 c.c. of methyl sulphate are added, and the mixture is stirred for 2 hours. The aqueous solution is poured from the ester, a further amount of water added, and the mixture heated on a water-bath for ½ hour. The ester is sufficiently pure for the oxidation.

Methyl cinnamate (20 g.) is dissolved in 1500 c.c. of ethyl alcohol and then cooled to − 40°. A solution of 24 g. of potassium permanganate in 800 c.c. of water is added gradually over 4 hours, with vigorous stirring. The precipitate of manganese dioxide is filtered off and the filtrate concentrated on the water-bath to about 200 c.c. The ester is hydrolysed by adding 20 g. of solid potash to the concentrated solution and keeping at room temperature for several hours. When the hydrolysis is complete, an excess of dilute sulphuric acid is added and the solution extracted several times with small volumes of ether, till about 3 l. of solvent have been used. Evaporation of the ether leaves about 15 g. of crude phenylglyceric acid. It is purified by solution in a small volume of methylal and precipitation with benzene. Slow evaporation of a concentrated aqueous solution gives the acid as large thin plates, m. p. 141° (Rüber, *Ber.*, 1915, **48**, 827).

A further method for the oxidation of unsaturated hydrocarbons, ethers, or acids to the corresponding glycol is the use of perhydrol in glacial acetic acid, which appears to be very convenient.

Preparation of Dihydroxystearic Acid from Oleic Acid.—To a solution of 12 g. of oleic acid in 80 c.c. of glacial acetic acid, 20 g. of concentrated hydrogen peroxide are added (36%) and the mixture is shaken occasionally till it becomes homogenous. This usually takes several days. The acetic acid is then distilled off in steam and the residue extracted with water and heated with an excess of *N*-sodium hydroxide for 6 hours. The acid recovered from the alkaline solution by acidification is purified by crystallisation from ethyl acetate. It then has m. p. 95°. Elaidic acid and palmitoleic acid and their esters are oxidised by a similar process to the corresponding dihydroxy acids and esters (Hilditch, *J.*, 1926, 1833).

This method has been applied successfully to the oxidation of allyl ethers for the formation of α-glyceryl ethers.

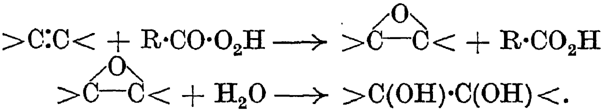
Preparation of a-Cetyl Glyceryl Ether.—Cetyl allyl ether (6 g.) (prepared by the action of cetyl chloride on a solution of sodium allyloxide) in 120 c.c. of glacial acetic acid is treated with 9·6 g. of perhydrol and heated on a steam-bath for 15 hours, further amounts of perhydrol being added at regular intervals till the equivalent of 9 mols. has been added.

When the solution is cold, it is neutralised by dilute aqueous ammonia and extracted with ether. The extract, after removal of the solvent, is heated with alcoholic potash to hydrolyse any acetyl compounds formed during the oxidation. *a*-Cetyl glyceryl ether is obtained by diluting the hydrolysed solution and extracting with ether. It is further purified by crystallisation from aqueous acetone and separates in rosettes of colourless needles, m. p. 64—65°. The yield of crude material is practically quantitative (Davies, Heilbron, and Owens, *J.*, 1930, 2545).

Glycols may also be prepared from some olefins by the action of a saturated solution of mercuric acetate (Balbiano and Paolini, *Ber.*, 1902, **35**, 2994; 1903, **36**, 3575). Lead tetra-acetate has also been used for the preparation of the glycol diacetates from some olefinic substances (Dimroth and Schweizer, *Ber.*, 1923, **56**, 1384). Sodium chlorate in aqueous solution containing a small amount of osmium tetroxide as a catalyst was originally proposed by K. A. Hofmann, Ehrhart, and Schneider (*Ber.*, 1913, **46**, 1657) for converting ethylenic compounds to saturated dihydroxy-compounds. The method has recently been applied with considerable success for the preparation of dihydroxy-acids from unsaturated acids.

Preparation of meso*Tartaric Acid from Maleic Acid.*—Sodium chlorate (113 g.) and maleic acid (86 g.) in 140 c.c. of water are mixed and heated to 50° after adding 10 c.c. of 1% solution of osmium tetroxide. (*Note.*—Osmium tetroxide is volatile and its vapour is extremely dangerous. Particular care should be taken to prevent the vapour coming in contact with the eyes by wearing gas-tight goggles.) After 9 hours' heating the solution is cooled, the catalyst removed by extraction with benzene and the aqueous solution exactly neutralised. The addition of barium chloride solution precipitates the tartaric acid as barium salt, which is collected, dried, and decomposed by warming for ½ hour with the calculated amount of dilute sulphuric acid The solution is filtered from barium sulphate and is evaporated in a tared dish on a steam-bath till the concentrated solution weighs approximately 1½ times the weight of tartaric acid expected. It is nucleated with a crystal of *meso*tartaric acid and kept in an ice-chest. The acid, which separates on keeping, is pure. The yield may amount to 90% of the theoretical. Fumaric acid yields *r*-tartaric acid by a similar process (Milas and Terry, *J. Amer. Chem. Soc.*, 1925, **47**, 1415). For further applications of this method see G. Braun, *ibid.*, 1929, **51**, 228; 1930, **52**, 3176, 3188.

The use of organic peracids for the conversion of ethylenic compounds into ethylene oxides and thence by hydrolysis into glycols has a wide application. The change may be represented thus :—



$$>C{:}C< + R\cdot CO\cdot O_2H \longrightarrow >\overset{O}{C{-}C}< + R\cdot CO_2H$$

$$>\overset{O}{C{-}C}< + H_2O \longrightarrow >C(OH)\cdot C(OH)<.$$

The oxidation is usually effected quite smoothly and in good yield. The resulting glycol is generally stereoisomeric with that obtained by oxidation with permanganate (Nametkin and Jarzeff, *Ber.*, 1923, **56**, 1803; Böeseken, *ibid.*, p. 2409).

Perbenzoic acid,* $C_6H_5CO\cdot O_2H$, is commonly used for this purpose, and the method consists essentially in adding a solution of the peracid of known concentration in chloroform or ether to the unsaturated substance, either at room temperature or cooled in a freezing mixture. When the oxidation is complete, the benzoic acid is removed by shaking with dilute alkali and the ethylene oxide isolated by evaporation of the solvent. The process is illustrated by the following examples.

Preparation of 4-*Methyl*cyclo*hexane Oxide and* 1 : 2-*Dihydroxy*-4-*methyl*cyclo*hexane.*—An ethereal solution of perbenzoic acid containing 4 g. of active oxygen is added to 25 g. of 4-methyl*cyclo*hexene. After keeping at room temperature for about 5 days, the ethereal solution is washed with dilute alkali, dried, and the solvent evaporated. The residue of 4-methyl*cyclo*hexane oxide is purified by distillation (yield 15—16 g., b. p. 147—148°/760 mm.).

The oxide is converted into the corresponding dihydroxy-compound by heating in a sealed tube at 110° with an excess of water for 4 hours. On cooling, the product is extracted with ether and the residue, after removing solvent from the ether extract, is distilled under reduced pressure, b. p. 131—132°/12 mm., m. p. after crystallisation 63—64° (Nametkin and Brüssoff, *Ber.*, 1923, **56**, 1807).

Preparation of Styrene Oxide.—To a solution of 44 g. of perbenzoic acid (0·33 mol.) in 500 c.c. of chloroform are added 30 g. of styrene (0·3 mol.). The solution is kept at 0° for 24 hours and is shaken frequently during the first hour. An aliquot portion should then be titrated to determine if all the styrene has reacted. When the oxidation is complete, the chloroform solution is shaken with 10% sodium hydroxide to remove benzoic acid, then washed with water and dried over anhydrous sodium sulphate. The removal of the solvent by distillation through a fractionating column leaves a residue of styrene oxide, b. p. 188—192°, yield 24—26 g. (Hibbert and Burt, *J. Amer. Chem. Soc.*, 1925, **47**, 2243; *Organic Syntheses*, 1928, **8**, 102).

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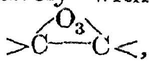
* Perbenzoic acid is comparatively unstable, but dry chloroform solutions may be kept for several days without any appreciable loss of activity. It is necessary to prepare the perbenzoic acid required in these oxidations from the commercially available and more stable benzoyl peroxide.

When the ethylene oxide is unstable, the dihydroxy-compound may be obtained directly by carrying out the oxidation in presence of water (G. Braun, *J. Amer. Chem. Soc.*, 1929, **51**, 229; compare Haworth, Hirst, Streight, Thomas, and Webb, *J.*, 1930, 2642).

Perbenzoic acid has been used also for converting glucal, lactal, and similar unsaturated derivatives of the sugars into ethylene oxides, and then by reaction with water or alcohol into sugars or their glucosides (M. Bergmann and Schotte, *Ber.*, 1921, **54**, 1564; M. Bergmann, *Annalen*, 1923, **434**, 79; Haworth, Hirst, Streight, Thomas, and Webb, *loc. cit.*).

Considerable differences have been found in the ease with which unsaturated compounds react with perbenzoic acid. Thus, while limonene is rapidly converted into the corresponding oxide, bornylene is attacked so slowly that it is best purified from associated impurities by treatment with perbenzoic acid (Meerwein, *J. pr. Chem.*, 1926, [ii], **113**, 18). Crotonic acid also reacts slowly with perbenzoic acid, while maleic acid appears to be indifferent (Böeseken, *Rec. trav. chim.*, 1926, **45**, 838; G. Braun, *loc. cit.*).

Some ethylene oxides prepared in this way are stable to hydrolysis. Böeseken and Elsen (*Rec. trav. chim.*, 1929, **48**, 363) recommend, in such circumstances, the use of peracetic acid, which gives acetates of the glycol as the product of oxidation. According to Arbusoff and Michailoff (*J. pr. Chem.*, 1930, [ii], **127**, 92), the normal product of the action of peracetic acid on an ethylenic compound is an ethylene oxide, and the glycol acetates result from its interaction with the acetic acid formed in the oxidation.

(b) *Formation of Ozonides.*—Ozone combines additively with ethylenic linkings to give ozonides of the general type,  $>\overset{O_3}{C\text{—}C}<$, and the further action of ozone converts these into perozonides.

The importance of the ozonides lies in their behaviour towards water. They are split more or less readily by this reagent into aldehydes, ketones and their peroxides, and acids, according to the circumstances. The fission always takes place between the carbon atoms which were joined by a double bond in the original compound. This furnishes a method for determining the position of a double bond in a compound, which is free from the uncertainty attached to use of alkaline or acid reagents. The general method of ozonisation consists in passing dry ozonised air or oxygen (from 1—15% ozone) into the unsaturated compound dissolved in a suitable solvent. Chloroform, carbon tetrachloride, hexane, ethyl acetate have been widely used as solvents for this purpose, while for low temperatures and for unstable ozonides ethyl chloride has many advantages. The passage of the ozonised air is continued till the solution contains no unchanged unsaturated compound. The solvent is then removed under reduced pressure. The crude ozonide thus obtained is usually a viscid oil with an unpleasant odour. Few ozonides only have been obtained crystalline.

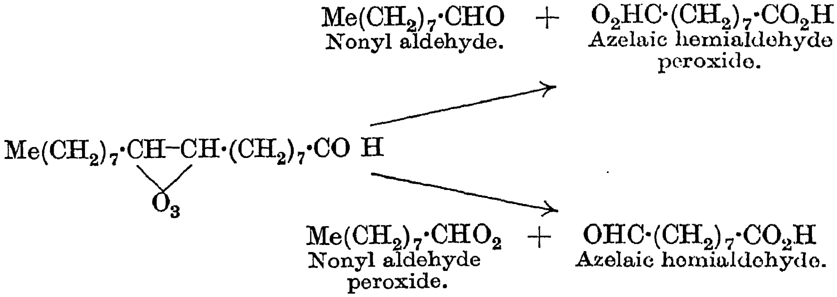
Ozonides should be treated with due caution, for some may explode violently on warming. In order to determine the position of the double bond, it is unnecessary to purify the ozonide. The crude product from the evaporation of the solvent from the ozonisation solution is treated with cold water or heated under reflux with water, according to its stability, and the products thus obtained are isolated and identified. Other methods of decomposing ozonides include treatment with glacial acetic acid or formic acid, or reduction with aluminium amalgam or sulphur dioxide or zinc dust (Harries and Neresheimer, *Ber.*, 1906, **39**, 2846; Harries and Franck, *ibid.*, 1909, **42**, 450; *Annalen*, 1910, **374**, 356; Harries and Haarmann, *Ber.*, 1915, **48**, 39). The more general method, however, is treatment with water. When the decomposition is complete, the product is examined for volatile aldehydes, ketones, acids, and carbon dioxide. Acetone is frequently present in the decomposition products as acetone peroxide—a volatile solid which appears as a sublimate in the condenser during the refluxing of the ozonide with water; acetone can be obtained from it by warming with aqueous sodium carbonate. The non-volatile products are first examined for their behaviour towards Fehling's solution, Schiff's reagent, and phenylhydrazine. The product is then extracted with ether, the acidic portion of the decomposition removed from the ether by washing with aqueous sodium bicarbonate, and the neutral and acidic portions are worked up separately. The aqueous solution remaining after ethereal extraction should be tested for oxalic acid.

For details of the process of ozonisation and descriptions of the apparatus used, the series of papers by Harries and his colleagues should be consulted (Harries, *Annalen*, 1905, **343**, 339; *ibid.*, 1910, **374**, 309; Harries and Weiss, *Ber.*, 1905, **37**, 3431; Harries, *ibid.*, 1907, **40**, 4905; Harries and v. Splawa Neymann, *ibid.*, 1908, **41**, 3552; Harries, *Annalen*, 1912, **390**, 235; Harries and Haarmann, *Ber.*, 1915, **48**, 32, 868; see also Dœuvre, *Bull. soc. chim.*, 1929, [iv], **45**, 140).

In order to illustrate the use of ozonisation in determining the structure of unsaturated acids the following description is given :—

The Preparation and Decomposition of the Ozonide of Oleic Acid.—A current of ozonised air or oxygen is passed through a solution of oleic acid in about 20 times its weight of chloroform until a portion of the solution ceases to decolorise bromine. The further action of ozone results in the formation of peroxide, but this does not affect the result. After removing the solvent under reduced pressure, the crude ozonide is heated under reflux with 4 times its weight of water for ½ hour. On cooling, the product is taken up in ether and the ethereal solution washed with water and sodium bicarbonate solution. The ethereal solution is dried over magnesium sulphate, the solvent removed, and the residue distilled under reduced pressure. Nonyl aldehyde and its peroxide is collected between 80° and 105°/71 mm., pelargonic acid, $CH_3\cdot(CH_2)_7\cdot CO_2H$, between 120° and 150°. The residue consists principally of the hemialdehyde of azelaic acid, $CHO\cdot(CH_2)_7\cdot CO_2H$. The sodium bicarbonate extract gives, on acidification, a solid consisting largely of azelaic acid, $CO_2H\cdot(CH_2)_7\cdot CO_2H$, its hemialdehyde and peroxide (Harries and Franck, *Ber.*, 1909, **42**, 454; Harries and Thieme, *ibid.*, 1906, **39**, 2844).

These decomposition products indicate quite clearly that the double bond in oleic acid is situated between the eighth and ninth carbon atoms of the carbon chain :—


Me(CH2)7·CHO + O2HC·(CH2)7·CO2H
Nonyl aldehyde.
Azelaic hemialdehyde peroxide.
Me(CH2)7·CH–CH·(CH2)7·CO H
O3
Me(CH2)7·CHO2 + OHC·(CH2)7·CO2H
Nonyl aldehyde peroxide.
Azelaic hemialdehyde.

Other examples of the use of this method in determining the position of double bonds in unsaturated acids are given by Linstead (*J.*, 1929, 2505) and Goldberg and Linstead (*ibid.*, 1928, 2354). For the use of the decomposition of ozonides in giving information on the position of double bonds, and for the separation and identification of the products, see Heilbron, Owens, and Simpson (*J.*, 1929, 879), Heilbron and Thompson (*ibid.*, p. 887), Harries (*Ber.*, 1904, **37**, 2708; 1905, **38**, 1195).

4. *Addition of Halogen.*

Bromine or chlorine combine additively with nearly all ethylenic compounds to give halogen-substituted saturated compounds :—

$$>C{=}C< + Br_2 \longrightarrow >CBr{\cdot}CBr<$$

The addition of bromine is effected quite smoothly and conveniently by adding the necessary amount of bromine—preferably dissolved in a suitable solvent—to the substance, which if it is solid should also be similarly dissolved. Carbon tetrachloride, chloroform, acetic acid, or carbon disulphide are generally employed. Sometimes the combination with bromine is achieved in aqueous solution, less frequently in ether, hexane, or even alcohol.

As the addition of bromine takes place quantitatively, and in dry indifferent solvents without any appreciable side reactions, it is possible to obtain a measure of the unsaturation of a hydrocarbon by determining the amount of bromine absorbed. For the abnormal behaviour of some unsaturated compounds to bromine see p. 26.

Determination of Unsaturation of Hydrocarbons.—Dry bromine (2 c.c.) is dissolved in about 750 c.c. of dry carbon disulphide or carbon tetrachloride, and the solution thus obtained is transferred to an amber-tinted bottle provided with a tight stopper. The concentration of the solution should be ascertained immediately before and at the end of each series of determinations, by treating a measured volume with an excess of aqueous potassium iodide and then titrating the liberated iodine with standard thiosulphate.

A weighed amount of the specimen (0·3—1·0 g.) is introduced into a dry stoppered flask and sufficient of the standardised bromine solution added to give a distinct red solution. The flask is closed, shaken, and then kept in a dark cupboard for 15 minutes. If sufficient bromine has been added, the solution should still be distinctly red at the end of this period. The excess of bromine is determined by adding an excess of potassium iodide and titrating the liberated iodine with thiosulphate (Allen, *Commercial Organic Analysis*, 1924, vol. II, p. 29; vol. III, p. 16).

The addition of chlorine is brought about either by passing the gas into the unsaturated compound in an indifferent solvent, or by adding a solution of chlorine in carbon tetrachloride of known concentration to the compound.

A further method which can be employed for this purpose is to bring the substances in contact in the vapour state. The olefin and the halogen are regulated so that the latter is not in large excess. In the case of ethylene this precaution is unnecessary, but the chloro- and bromo-derivatives of propylene and the butylenes are more sensitive to the action of an excess of free halogen. A more convenient method is to prepare some of the liquid dihalogen compounds by mixing the halogen with the olefin, and then to pass the olefin into the liquid thus obtained and cool in a freezing mixture. Chlorine or bromine is then introduced cautiously so that it is never in excess. By such a process the substituting action of the halogen is reduced to a minimum (Hickinbottom and Ryder, *J.*, 1931, 1285).

Iodine, in contrast to chlorine and bromine, shows only a slight tendency towards addition at the double bond. It only forms di-iodo-compounds with a few ethylenic compounds like styrene, allyl alcohol. Although iodine itself has little tendency to combine, iodine monochloride reacts normally, yielding iodo-chlorides. The use of this reagent in determining the " unsaturation " of fatty acids and fats is referred to elsewhere (p. 212).

Thiocyanogen has been found to combine additively with some unsaturated compounds. Its action appears to be intermediate between that of bromine and that of iodine (see Kaufmann and Liepe, *Ber. deut. pharm. Ges.*, 1923, **33**, 139; Challenger, A. L. Smith, and Paton, *J.*, 1923, **123**, 1055; Challenger and Bott, *ibid.*, 1925, **127**, 1039; Söderbäck, *Annalen*, 1925, **443**, 142).

5. *Addition of Halogen Hydrides.*

Unsaturated compounds combine more or less readily with halogen hydride according to the general scheme :—

$$>C{=}C< + \text{H Hal} \longrightarrow >CH{\cdot}C(\text{Hal})<$$

This reaction occurs so that the halogen is added to the carbon atom combined with the fewest hydrogens. Thus, hydrogen bromide converts propylene into *sec.*-propyl bromide; *iso*butylene yields *tert.*-butyl bromide. With the arylolefins a similar orientation of the halogen appears to take place, for styrene, $PhCH{:}CH_2$, gives $PhCHBr{\cdot}CH_3$. This generalisation is, however, only approximately true, since in such additions smaller or greater amounts of the isomeric halogen compound are formed (Michael, *J. pr. Chem.*, 1899, [ii], **60**, 446; Michael, *ibid.*, 348; Ipatieff and Ogonofski, *Ber.*, 1903, **36**, 1988; Ingold and Ramsden, *J.*, 1931, 2746; Ingold and H. G. A. Smith, *ibid.*, p. 2752). Recently, it has been found that the orientation of the halogen in the addition product may be determined by the presence of peroxides or air. Thus the reaction of allyl bromide with hydrogen bromide furnishes 1 : 3-dibromopropane in the presence of air or peroxides, while if precautions are taken to ensure their absence, 1 : 2-dibromopropane results (Kharasch and Mayo, *J. Amer. Chem. Soc.*, 1933, **55**, 2468). Similar observations have been made for propylene, vinyl bromide, γ : γ-dimethyl-Δ^{α}-pentene, undecenoic acid and its ethyl ester, and for undecenyl acetate (Kharasch, McNab, and Mayo, *J. Amer.. Chem. Soc.*, 1933, **55**, 2521, 2531; Kharasch, Hannum, and Gladstone, *ibid.*, 1934, **56**, 244; Ashton and J. C. Smith, *J.*, 1934, 435, 1308; compare Kharasch and Hinckley, *J. Amer. Chem. Soc.*, 1934, **56**, 1212; Kharasch, Hinckley, and Gladstone, *ibid.*, p. 1642; Kharasch and Hannum, *ibid.*, p. 178). The magnitude of the effect, however, would appear to depend on the unsaturated compound (Ashton and Smith, *loc. cit.*, p. 1308; Linstead and Rydon, *J.*, 1934, 2001).

The combination with halogen hydride is not confined to the olefins; unsaturated acids and ketones show a similar behaviour. With these compounds, however, the halogen takes up a position remote from the carbonyl group, at least with the $\alpha\beta$- and $\alpha\gamma$-unsaturated acids and ketones (Fittig and Messerschmidt, *Annalen*, 1881, **208**, 94; Fittig, *ibid.*, 1889, **255**, 30).

The addition may be effected by more or less prolonged contact of the unsaturated compound with a concentrated aqueous solution of the halogen hydride, or more conveniently by using a saturated solution of the halogen hydride in glacial acetic acid. The speed with which the reaction takes place depends on the nature of the unsaturated compound and also on the halogen hydride employed. In general hydrogen iodide combines more readily than hydrogen bromide, which is more reactive than hydrogen chloride. When the reaction takes place only slowly at room temperature, the rate may be accelerated by warming in closed vessels. For the experimental details the following papers should be consulted: Berthelot, *Annalen*, 1857, **104**, 184; 1860, **115**, 115; Schorlemmer, *ibid.*, 1873, **166**, 177; Ipatieff and Ogonofski, *loc. cit.*; Maire, *Bull. Soc. chim.*, 1908, [iv], **3**, 280; Michael and Brunel, *Amer. Chem. J.*, 1912, **48**, 267; Vorländer and Eichwald, *Ber.*, 1923, **56**, 1153; Ingold, *loc. cit.*

With unsaturated compounds of the terpene series, the addition of halogen hydride proceeds readily. The products, in many cases, are crystalline, and serve to characterise the terpenes. The procedure consists in passing a stream of the dried halogen hydride either into the terpene or more usually into a solution in acetic acid or ether.

The preparation of limonene bis-hydrochloride illustrates the method.

Preparation of Limonene Bis-hydrochloride.—A stream of dry hydrogen chloride is passed over limonene diluted with half its volume of acetic acid. The solution is shaken frequently to facilitate the absorption of the gas. As soon as the mass solidifies, it is washed with water, drained on a porous tile, and purified by crystallisation from aqueous alcohol. When pure it melts at 50—51°.

Dipentene bis-hydrochloride is prepared similarly.

Wallach (*Annalen*, 1887, **239**, 25) describes the preparation of sylvestrene bis-hydrochloride and terpinene bis-hydrochloride (*ibid.*, 1906, **350**, 147).

By working in carbon disulphide or light petroleum solution the terpenes which give bis-hydrochlorides may be made to yield monohydrochlorides (Wallach, *Annalen*, 1892, **270**, 189; Wallach and Boedecker, *ibid.*, 1907, **356**, 198).

6. *Addition of Hypochlorous, Hypobromous, and Hypoiodous Acids.*

These acids unite directly with the olefinic linking to give halogen hydrins according to the following scheme :—

$$>C{:}C< + \mathrm{HO{\cdot}Hal} \longrightarrow >C(OH){\cdot}C(Hal)< \qquad (\mathrm{Hal} = \mathrm{Cl, Br\ or\ I.})$$

For the preparation of chlorohydrins, a dilute solution of hypochlorous acid is kept in contact with the unsaturated compound till the combination is complete. Solutions of hypochlorous acid for this purpose may conveniently be prepared by the method described by Wohl and Schweitzer (*Ber.*, 1907, **40**, 94; compare Graebe, *ibid.*, 1902, **35**, 2753). Experimental details are given by Michael and Leighton (*Ber.*, 1906, **39**, 2157), Carius (*Annalen*, 1863, **126**, 197), Pauly and Neukam (*Ber.*, 1908, **41**, 4155); compare Henry (*Bull. Acad. roy. Belg.*, 1906, 523). Erlenmeyer and Lipp (*Annalen*, 1883, **219**, 185), Glaser (*ibid.*, 1868, **147**, 79), and Albitzki (*J. pr. Chem.*, 1900, [ii], **61**, 66) give examples of the reaction of unsaturated acids with hypochlorous acid.

Aqueous solutions of hypobromous acid—prepared by the addition of bromine to an aqueous suspension of mercuric oxide—behave similarly. The addition of the elements of hypobromous acid to unsaturated acids can in many instances be achieved by the reaction of the alkali salt of the acid with bromine water (Lossen, Dueck, and Leopold, *Annalen*, 1906, **348**, 285).

Preparation of β-Bromo-β-phenylhydroxypropionic Acid.—Cinnamic acid (30 g.) suspended in 400 c.c. of water is neutralised by the addition of 28 g. of potassium carbonate, and after cooling to 4° a solution of 32 g. of bromine and 57 g. of crystalline sodium carbonate in 500 c.c. of water is added. After half an hour the solution is filtered and then acidified by the addition of 50 c.c. of concentrated hydrochloric acid. A precipitate consisting principally of unchanged cinnamic acid is obtained. The filtrate is extracted with ether to remove the required bromohydroxy acid, which is obtained as a crystalline solid by evaporation of the ether. It is purified by several crystallisations from chloroform, m. p. 125° (Riiber and Berner, *Ber.*, 1921, **54**, 1954).

The preparation of bromohydrins from unsaturated hydrocarbons and ethers has been simplified by the discovery by Read and his collaborators that olefins react with dilute solutions of bromine in water to give a high proportion of the bromohydrin.

Preparation of β-Bromoethyl Alcohol.—A current of air charged with bromine is passed into water through which ethylene is bubbling. When all the bromine has combined, the liquid is neutralised with sodium carbonate and the insoluble dibromoethane separated. The aqueous portion and the aqueous washings of the dibromide are combined and extracted with ether. The solvent is removed from the extract after drying. The residue of crude β-bromoethyl alcohol is distilled under reduced pressure; the pure compound is collected at 145—149°. The yield from 450 g. of bromine in 1500 c.c. of water is 120 g. (Read and Williams, *J.*, 1917, **111**, 240; 1920, **117**, 359).

Amylene also yields the bromohydrin by the action of aqueous bromine (Read and Reid, *J.*, 1928, 1488). Styrene, anethole, *iso*-safrole react in the same way at 90° with aqueous bromine to furnish principally the corresponding bromohydrin. Indene furnishes the corresponding bromohydroxy-compound by the gradual action of bromine on a suspension of the hydrocarbon in water (Pope and Read, *J.*, 1912, **101**, 760; Read and Hurst, *ibid.*, 1922, **121**, 2552).

The addition of the elements of hypoiodous acid is effected conveniently by the addition of the necessary amount of iodine to a moist ethereal solution of the unsaturated compound containing mercuric oxide in suspension. The ether must be free from alcohol. By using alcohol as the solvent this method can be employed to prepare bromo ethers. If acetic anhydride be added to the ethereal solution before adding the iodine, it can also be used for the preparation of iodoacetates (Brunel, *Bull. Soc. chim.*, 1905, [iii], **33**, 382).

*Preparation of 2-Iodo*cyclo*hexanol.*—*cyclo*Hexene (40 g.) diluted with 150 c.c. of ether—free from alcohol—is shaken with 8 c.c. of water and 55 g. of mercuric oxide, while 124 g. of iodine are gradually added, the mixture being cooled. When the colour of the iodine has disappeared, the suspended matter is collected and the ethereal solution shaken with a solution of potassium iodide and bisulphite. It is then dried and the solvent evaporated, leaving the iodohydrin as an oil which slowly crystallises. It is purified by crystallisation from light petroleum: it melts at 42° (Brunel, *Ann. chim.*, 1905, [vii], **6**, 219).

7. *Addition of Nitrosyl Chloride and Oxides of Nitrogen.*

Nitrosyl chloride or bromide unite directly with the double linking of most unsaturated hydrocarbons to give compounds which can be represented by the general formula $>\mathrm{C(NO){\cdot}C(Cl)}<$. The addition compounds thus produced are in many instances crystalline and characteristic of the unsaturated compound yielding them. Although these compounds are formulated as nitroso-compounds, most of them are colourless owing to polymerisation to a dimeric form, and perhaps also to isomerisation of the nitroso-group to the $=\mathrm{N{\cdot}OH}$ grouping. Nitroso-chlorides derived from unsaturated compounds containing no hydrogen attached to the unsaturated carbon atoms appear to be exceptions, for $\mathrm{(CH_3)_2C(NO){\cdot}CCl(CH_3)_2}$ and similar substances are blue.

The combination of nitrogen trioxide and of nitrogen tetroxide with unsaturated hydrocarbons results generally in the formation of compounds, similar in type to the nitrosochlorides. Nitrogen tetroxide gives nitrosates (I); nitrogen trioxide yields nitrosites (II):

$$\underset{\text{(I.)}}{>C(NO)\cdot C(NO_3)<} \qquad \underset{\text{(II.)}}{>C(NO)\cdot C(NO_2)<} \qquad \underset{\text{(III.)}}{>C(NO_2)\cdot C(NO_2)<}$$

These substances are generally colourless and crystalline; they are frequently used to characterise unsaturated hydrocarbons.

It should be noted that nitrogen tetroxide may yield a dinitro-compound (III) as the principal product with substances such as diphenylbutadiene and dibenzalacetone.

Nitrosochlorides, nitrosites, and nitrosates react with aniline, piperidine, and other primary and secondary amines; the halogen, $—NO_2$, or $—NO_3$ group being replaced by the amine residue to give nitroso amino-compounds or nitrolamines of the general type $>C(NO)\cdot C(NHR)<$. Most nitrolamines crystallise well and serve to identify unsaturated compounds which do not give characteristic nitrosohalides, nitrosites, or nitrosates.

The preparation of nitrosochlorides as a method of characterising terpenes and other unsaturated compounds was introduced by Tilden and his co-workers (Tilden and Shenstone, *J.*, 1877, **31**, 554; Tilden and Forster, *ibid.*, 1894, **65**, 324). Their procedure consisted in passing nitrosyl chloride into a well-cooled solution of the unsaturated compound in three or four times its bulk of chloroform. The product was precipitated by the addition of methyl alcohol. A more convenient method is to use a mixture of the unsaturated compound and amyl or ethyl nitrite in a suitable solvent as acetic acid or alcohol, and to add concentrated or fuming hydrochloric acid cautiously to the well-cooled solution.

Preparation of Pinene Nitrosochloride.—Pinene (7 c.c.), amyl nitrite (10 c.c.), and glacial acetic acid (15 c.c.) are mixed and cooled in a freezing mixture. A well-cooled mixture of 5·5 c.c. of concentrated hydrochloric acid in an equal volume of glacial acetic acid is added gradually and with efficient stirring. A blue colour develops which should disappear before each further addition of the acid. The nitrosochloride separates as a white crystalline powder which can be purified from chloroform solution by the addition of methyl alcohol. It is crystallised from benzene.

The nitrosobromide is obtained by substituting the hydrochloric acid by hydrobromic acid. Limonene and dipentene nitrosochlorides are prepared by a similar method (Wallach, *Annalen*, 1888, **245**, 251).

Preparation of Trimethylethylene Nitrosochloride.—Fuming hydrochloric acid (20 c.c.) is added slowly to a cooled mixture of 14 g. of trimethylethylene and 20 c.c. of amyl nitrite. The solution is stirred during the addition of the acid. The liquid becomes blue immediately and then slowly solidifies to a white paste of crystals. The solid matter is collected, washed with water and then with ice-cold alcohol till the odour of amyl nitrite disappears. The nitrosochloride thus obtained is dried on a porous tile; yield 4—7 g., m. p. 74—75°, to a blue liquid.

The nitrosochloride is readily soluble in most solvents except alcohol. Its solutions are colourless, or at the most have a faint green colour, at room temperature. On warming to 35° they become bluish-green owing to dissociation to the monomeric form. This form may be obtained pure by warming a solution of 3 g. of the nitrosochloride in 50 c.c. of ether for 20—30 minutes under reflux. A blue residue of the monomeric form remains on distilling off the ether. It rapidly polymerises to the dimeric form, m. p. 74—75°.

Preparation of Dipentene Nitrosate.—3·5 G. of concentrated nitric acid (d 1·4) are added slowly to a mixture of 5 g. of dipentene, 4 c.c. of amyl nitrite, and 2 c.c. of acetic acid. The solution must be cooled by immersion in a freezing mixture and stirred during the addition of the nitric acid. After keeping for some time, alcohol is added till the solution is homogeneous. The solution is kept in a freezing mixture. Crystals which gradually separate on keeping are collected, washed with alcohol, and crystallised by slow evaporation from benzene.

Preparation of Trimethylethylene Nitrosate.—A slow stream of nitrogen peroxide (generated from lead nitrate) is passed into a solution of 20 g. of trimethylethylene in 60 c.c. of ether, cooled in freezing mixture. The solution becomes green, and after some time a small quantity of white crystals separate. They are collected, and consist of bimolecular trimethylethylene nitrosate, m. p. 98—99°, yield 2—6 g.

The ethereal filtrate, after removal of the bimolecular nitrosate, is washed ten or twelve times with water, dried over anhydrous sodium sulphate, and then cautiously evaporated over a warm water-bath. A blue-green liquid remains (yield 30—35 g.), consisting of crude monomolecular trimethylethylene nitrosate (Schmidt, *Ber.*, 1902, **35**, 2336).

Preparation of cyclo*Hexene Nitrosite.*—A concentrated aqueous solution of 1 g. of sodium nitrite is covered with 1 g. of *cyclo*hexene and 1 g. of light petroleum. It is cooled and a solution of 1 g. of acetic acid added.

The nitrosite soon separates in white flocks; a further amount is obtained after adding more sodium nitrite and acetic acid and keeping for some days. The nitrosite is purified by solution in chloroform and precipitation with methyl alcohol (Baeyer, *Annalen*, 1894, **278**, 108).

Preparation of Trimethylethylene Nitrosite.—A slow stream of nitrous fumes (from 80 g. of nitric acid and 10 g. of arsenious acid) is passed into a solution of 20 g. of trimethylethylene in 60 c.c. of ether. The temperature must be kept below 10° by cooling in a bath of ice and salt, and if necessary by interrupting the stream of gas. When the odour of the hydrocarbon has become faint, the ethereal solution is washed several times with water, until it has a pure blue colour. After drying over anhydrous sodium sulphate, the solution is evaporated carefully over a warm water-bath. A pure blue liquid remains, and it is freed from traces of ether and olefin by keeping in a partial vacuum over sulphuric acid and potassium hydroxide at 0°. It polymerises in the dark in one or two days at the ordinary temperature to a white crystalline solid, m. p. 75°. It is depolymerised by warming at 75°.

For the constitution of these compounds see J. Schmidt (*Ber.*, 1902, **35**, 2323, 2336, 3721, 3727, 3737; 1903, **36**, 1765, 1768), Wieland (*Annalen*, 1903, **329**, 225; 1907, **353**, 65; 1921, **424**, 71; *Ber.*, 1904, **37**, 1524).

Preparation of Trimethylethylene Nitrolaniline.—Aniline (9 c.c.) in 15—20 c.c. of alcohol is heated for a few moments with 8 g. of trimethylethylene nitrosate. A vigorous reaction sets in, during which the nitrosate disappears. The clear solution is poured into a dish, and water added till a precipitate just forms. In a short time the vessel is filled with a mass of crystals of the nitrolamine. They are purified by crystallisation from alcohol, m. p. 140—141° (Wallach, *Annalen*, 1887, **241**, 296).

Preparation of Pinene Nitrolpiperidine.—Pinene nitrosochloride is warmed with an excess of 80% piperidine. After the vigorous reaction has subsided, the addition of water precipitates the nitrolpiperidine, m. p. 118—119° (Wallach, *Annalen*, 1888, **245**, 253).

Nitric acid can combine additively with some unsaturated hydrocarbons according to the scheme :—

$$>C{:}C< + HNO_3 \longrightarrow >C(OH){\cdot}C(NO_2)<.$$

The product isolated from the reaction may not be the simple hydroxynitro-compound. It may be either the corresponding nitric ester or the dehydration product. Thus αα-diphenylethylene, $Ph_2C{:}CH_2$, reacts with anhydrous nitric acid in carbon tetrachloride to give the nitro-alcohol $Ph_2C(OH){\cdot}CH_2NO_2$. Trimethylethylene, under similar conditions, gives the nitro-olefin $(CH_3)_2C{:}C(NO_2)CH_3$, formed probably by the dehydration of the corresponding nitro-alcohol. By treatment with a mixture of nitric acid and sulphuric acid, ethylene yields the nitrate of β-nitroethyl alcohol in addition to ethylene glycol dinitrate (Wieland and Sakellarios, *Ber.*, 1920, **53**, 201; Wieland and Rahn, *ibid.*, 1921, **54**, 1770). Gunter

8. *Other Additive Reactions.*

(1) *Sulphurous Acid and Bisulphites, Arylsulphinic Acids.*—Unsaturated hydrocarbons, as amylene, *cyclo*hexene, pinene, dipentene, combine with the elements of sulphurous acid on shaking with solutions of bisulphite, to give as principal product the corresponding sulphonic acid (Kolker and Lapworth, *J.*, 1925, **127**, 307).

Some unsaturated acids, aldehydes, and ketones containing the grouping $>C{:}\underset{|}{C}{\cdot}CO$ react similarly to give β-sulphonic acids (Valet, *Annalen*, 1870, **154**, 63; Labbé, *Bull. Soc. chim.*, 1899, [iii], **21**, 1077; Messel, *Annalen*, 1871, **157**, 15; Müller, *Ber.*, 1873, **6**, 1441; Heusler, *ibid.*, 1891, **24**, 1805; Tiemann, *ibid.*, 1898, **31**, 3304; Knoevenagel, *ibid.*, 1904, **37**, 4038). With the aldehydes and many ketones, the product is the sulphonate of the bisulphite compound.

The combination of benzenesulphinic acid with some αβ-unsaturated acids and ketones has been described by Kohler and Reimer (*Amer. Chem. J.*, 1904, **31**, 163).

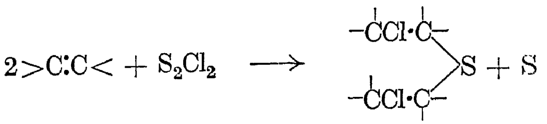
(2) *Hydrogen Sulphide and Mercaptans.*—There are few recorded examples of the combination of hydrogen sulphide with the ethylenic grouping; it appears to be confined to unsaturated ketones.

Mercaptans, however, are more reactive, for in suitable circumstances they are able to combine with some unsaturated hydrocarbons as well as with unsaturated ketones and acids. This reaction is generally brought about by the action of a catalyst as hydrochloric or sulphuric acid, although some addition compounds have been obtained merely by mixing the mercaptan and the unsaturated compound (Posner, *Ber.*, 1904, **37**, 502; 1907, **40**, 4788; Posner and Tscharno, *ibid.*, 1905, **38**, 646).

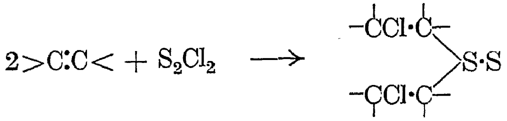
Ruhemann (*J.*, 1905, **87**, 17, 461) recommends piperidine as a condensing agent for the combination of unsaturated ketones with mercaptans, so as to prevent reaction of the carbonyl group with the mercaptan.

(3) *Sulphur Monochloride.*—The interaction of sulphur chloride with some unsaturated compounds has been examined in detail by Gibson and Pope (*J.*, 1920, **117**, 271) and by Pope and Smith (*ibid.*, 1921, **119**, 396; 1922, **121**, 1166). Addition occurs with ethylene and its immediate homologues, with styrene and with allyl chloride

to yield halogen-substituted sulphides or, in some instances, disulphides :—


(I.)

or


(II.)

Ethylene, propylene, and β-butylene and styrene react according to the equation (i); trimethylethylene, β-methyl-Δ^{β}-butylene, and allyl chloride at low temperatures give disulphides, but at higher temperatures combination takes place to give the sulphide.

(4) *Aromatic Hydrocarbons, Phenols, and Aromatic Amines.*—Toluene, ψ-cumene, and the xylenes react with styrene in the presence of concentrated sulphuric acid to give diarylethanes (Kraemer, Spilker, and Eberhardt, *Ber.*, 1890, **23**, 3269). A more convenient technique, which has been applied to the combination of gaseous olefins with aromatic hydrocarbons, employs aluminium chloride as the catalyst (Balsohn, *Bull. Soc. chim.*, 1879, [ii], **31**, 529; Essner, *ibid.*, 1881, [ii], **36**, 212; Milligan and Reid, *J. Amer. Chem. Soc.*, 1922, **44**, 206).

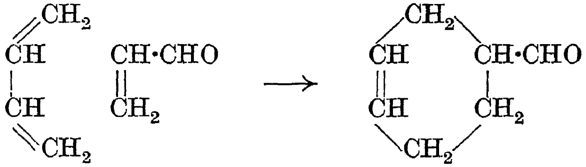
In the presence of a suitable catalyst, phenol combines comparatively easily with unsaturated hydrocarbons to give as the principal product a *para*-substituted phenol. Among the unsaturated compounds which have been used are *iso*amylene, styrene, dihydronaphthalene, *cyclo*hexene, octahydronaphthalene, and the methyl*cyclo*hexenes. The combination has been brought about by zinc chloride, by sulphuric acid in glacial acetic acid, or by hydrochloric acid (Königs, *Ber.*, 1890, **23**, 3144; 1891, **24**, 179, 3889; Schrauth and Quasebarth, *ibid.*, 1924, **57**, 854).

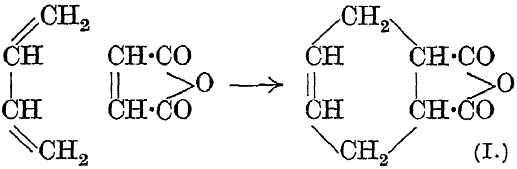
Recently, aniline has been found to undergo a similar additive reaction with unsaturated hydrocarbons in the presence of aniline hydrobromide to give substituted anilines as the principal product. Secondary amines are produced at the same time, showing that the amino group is able to combine with the double bond in olefins (Hickinbottom, *J.*, 1932, 2646; 1934, 319, 1981).

(5) Other substances which can combine with unsaturated hydrocarbons, either alone or under the influence of a catalyst, are nitrogen trichloride (Coleman and Howells, *J. Amer. Chem. Soc.*, 1923, **45**, 3084); alkali metals (Schlenck, Appenrodt, Michael, and Thal, *Ber.*, 1914, **47**, 473); mercury salts (K. A. Hofmann and Sand, *ibid.*, 1900, **33**, 1340, 2692; Sand, *ibid.*, 1901, **34**, 1385, 2906; Schöller, Schrauth, and Essers, *ibid.*, 1913, **46**, 2864); acyl chlorides (Wieland and Bettag, *ibid.*, 1922, **55**, 2246).

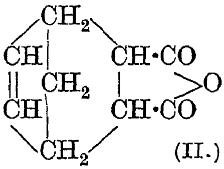
(6) Diels and his collaborators have examined in detail a number

of extremely interesting reactions between unsaturated compounds, such as quinones, unsaturated aldehydes, unsaturated acids, their esters and anhydrides, with compounds containing conjugated double linkings such as butadiene, isoprene, *cyclo*pentadiene, and even heterocyclic compounds as furane and pyrrole (Diels, Blom, and Koll, *Annalen*, 1925, **443**, 242; Diels and Alder, *ibid.*, 1929, **470**, 62; 1931, **490**, 236; *Ber.*, 1929, **62**, 2081; Diels, Alder, and Stein, *ibid.*, 1929, **62**, 2337). Except in a few cases, the addition occurs with the formation of a six-membered ring. The following examples illustrate this :—





(I.)



(II.)

Cyclic unsaturated compounds containing a conjugated system of double bonds, such as *cyclo*pentadiene and fulvenes, *cyclo*hexadiene, furane react in the same way as butadiene. Thus *cyclo*pentadiene and maleic anhydride furnish (II). The addition of dienes to quinones is discussed on p. 186.

Addition of Butadiene to Maleic Anhydride : Formation of Δ^4-*Tetrahydrophthalic Anhydride* (I).—A solution of about 2—2½ g. of butadiene in 10 c.c. of pure benzene is mixed with 4 g. of maleic anhydride and kept overnight in a sealed tube. It is then heated at 100° for 5 hours. On cooling, a white paste of crystals is obtained. It is collected by filtration and purified by crystallisation from hot light petroleum (b. p. 60—80°), m. p. 103—104°. On boiling with water it yields *cis*-tetrahydrophthalic acid, m. p. 166°.

Addition of Maleic Anhydride to cyclo*Pentadiene : Formation of* 3 : 6-*Endomethylene*- Δ^4-*tetrahydrophthalic Anhydride* (II).—*cyclo*Pentadiene (1 mol. prop.) is gradually added to a cooled suspension of maleic anhydride (1 mol. prop.) in 5 times its weight of benzene. Reaction commences immediately with the evolution of heat. The anhydride dissolves and the product commences to separate even before all the *cyclo*pentadiene has been added. The product is collected by filtration and purified by crystallisation from boiling light petroleum m. p. 164—165°.

The acid, m. p. 177—178°, is formed by boiling with water.

9. *The Influence of Structure and other Factors on Additive Reactions.*

The rate of addition of bromine to a double bond in non-aqueous solvent appears to be determined by a number of factors—(1) the position of the double bond with respect to the rest of the molecule,

(2) the nature of other groups present, (3) the solvent, and (4) the presence of catalysts. A number of qualitative observations have been made which show that the accumulation of negative groups may so retard the rate of bromination that the dibromide cannot be isolated or its formation detected. The groups which have the most pronounced effect are phenyl, halogens, carboxyl, or carbalkoxyl. Thus $CCl_2{:}CCl_2$, $C_6H_5CCl{:}CClC_6H_5$, $PhCBr{:}CBrPh$, $Ph_2C{:}CHBr$, $Ph_2C{:}CBrMe$, $Ph_2C{:}CPh_2$, bromomesaconic acid, and dibromofumaric acid, $(CO_2H)CBr{:}CBr(CO_2H)$, are among those reported not to combine with bromine (compare Bauer, *Ber.*, 1904, **37**, 3317; *J. pr. Chem.*, 1905, [ii], **72**, 201).

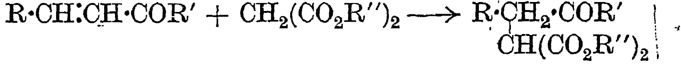
More exact information of the retarding effect of these groups is afforded by determination of the rates of reaction. The results are most complete for the unsaturated acids, and it appears that unsaturated acids containing a carboxyl group attached to one of the unsaturated carbon atoms, react more slowly than those in which the carboxyl group is attached to a saturated carbon. Even this generalisation is subject to some exceptions. Although cinnamic acid and its methyl and ethyl esters combine but slowly with bromine in carbon tetrachloride, *o*-methoxycinnamic acid combines extremely rapidly. The influence of the position of substituents on the reactivity of derivatives of cinnamic acid is seen also in the behaviour of α-phenylcinnamonitrile and its nitro-derivatives. The unsubstituted nitrile combines with bromine with difficulty, while α-phenyl-*p*-nitrocinnamonitrile forms no additive compound with bromine. The corresponding *ortho* and *meta* nitro-compounds react with bromine (Williams and T. C. James, *J.*, 1928, 344; Sudborough and John Thomas, *ibid.*, 1910, **97**, 715, 2450).

Catalysts further influence the addition of bromine; hydrogen halides, moisture, and iodine have definite effects, while exposure to light also accelerates the addition. Further, the solvent also appears to have an effect, the addition of bromine to cinnamic acid being more rapid in carbon disulphide solution than in carbon tetrachloride (compare Ley, *Ber.*, 1917, **50**, 243; Piutti and Calcagni, *Rend. Accad. Sci. Fis. Mat. Napoli*, 1909, [iii], **15**, 18; Abati, *Gazzetta*, 1908, **37**, [ii], 577; Vorländer and Siebert, *Ber.*, 1906, **39**, 1029).

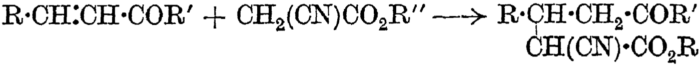
Although >CO and >CN groups have the effect of retarding combination of bromine with an ethylene linking situated adjacent to them, it appears that these groups enhance the reactivity of the double bond towards some reagents which have little or no tendency to combine additively with ethylene hydrocarbons. Among such substances are conjugated compounds, hydrogen cyanide, hydroxylamine, semicarbazide, ammonia, and amines, malonic ester, acetoacetic ester, cyanoacetic ester, and the like. These compounds add themselves to unsaturated nitriles, acids and their esters, ketones and aldehydes containing the grouping $>C{:}\underset{|}{C}\cdot\underset{|}{C}O$ or $>C{:}\underset{|}{C}\cdot CN$.

These reactions are of considerable importance in organic syntheses and a short summary of typical combinations is given.

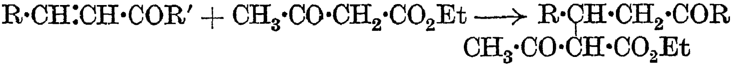
(a) *Malonic Ester, Cyanoacetic Ester, Acetoacetic Ester, etc.*, react with αβ-unsaturated ketones and esters under the influence of sodium ethoxide, diethylamine, or piperidine :—

(1) 

$$R\cdot CH{:}CH\cdot COR' + CH_2(CO_2R'')_2 \longrightarrow R\cdot\underset{CH(CO_2R'')_2}{C}H_2\cdot COR'$$

(2) 

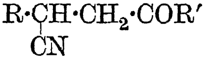
$$R\cdot CH{:}CH\cdot COR' + CH_2(CN)CO_2R'' \longrightarrow R\cdot\underset{CH(CN)\cdot CO_2R''}{C}H\cdot CH_2\cdot COR'$$

(3) 

$$R\cdot CH{:}CH\cdot COR' + CH_3\cdot CO\cdot CH_2\cdot CO_2Et \longrightarrow R\cdot\underset{CH_3\cdot CO\cdot CH\cdot CO_2Et}{C}H\cdot CH_2\cdot COR$$

where R′ = alkyl, aryl, or OAlk.

(b) *Hydrogen Cyanide.*—The addition takes place with αβ-unsaturated acids and their esters, αβ-unsaturated nitriles, and ketones to give β-cyano-compounds of the general type,



$$R\cdot\underset{CN}{C}H\cdot CH_2\cdot COR'$$

(Bredt and Kallen, *Annalen*, 1896, **293**, 350; Claus, *ibid.*, 1878, **191**, 33; Lapworth, *J.*, 1904, **85**, 1214; Lapworth and McRae, *ibid.*, 1922, **121**, 1699; Higginbotham and Lapworth, *J.*, 1922, **121**, 49).

This reaction is of importance as it provides a method of preparing substituted succinic acids by the hydrolysis of the nitriles thus prepared.

Preparation of Methylsuccinic Acid from Ethyl Crotonate.—Ethyl crotonate (5 g.) dissolved in 20 c.c. of alcohol is heated on a steam-bath after adding potassium cyanide (3 g. in 6 c.c. of water). The solution becomes yellow and some ammonia is evolved. After 4 hours an excess of baryta solution is added and the heating continued till ammonia ceases to be evolved. The whole is evaporated to dryness and heated with concentrated nitric acid to destroy any unchanged crotonic acid. After removing the excess of nitric acid, the residue is extracted with ether. Evaporation of the ethereal solution gives 5 g. of crude methylsuccinic acid, which is purified by washing with chloroform (Higginbotham and Lapworth, *loc. cit.*).

(c) *Ammonia, Amines, Hydroxylamine, Phenylhydrazine, and Semicarbazide.*—αβ-Unsaturated acids are, in general, able to unite with ammonia, aniline and its homologues, hydroxylamine to give an amide or salt of a β-substituted acid. The method is suited to the preparation of β-amino-acids, and the method of preparation is illustrated by the following example :—

Preparation of β-Aminobutyric Acid.—40 G. of crotonic acid and 400 c.c. of 25% aqueous ammonia are heated in an autoclave for 24 hours at 140°. The product is evaporated on the water-bath and then evaporated several times with alcohol till a crust forms on the surface. The product is then triturated with alcohol giving a white crystalline paste. After keeping in the ice-chest for 12 hours the β-amino-acid is collected and the filtrate evaporated to obtain a further quantity. The yield of β-aminobutyric acid can be increased by subjecting the filtrate from the second crop to another treatment with 400 c.c. of aqueous ammonia in an autoclave (Scheibler, *Ber.*, 1912, **45**, 2278; compare E. Fischer and Röder, *ibid.*, 1901, **34**, 3755).

The addition of aniline to αβ-unsaturated acids is effected similarly by heating the acid with the aniline (Autenrieth and Pretzell, *Ber.*, 1903, **36**, 1262).

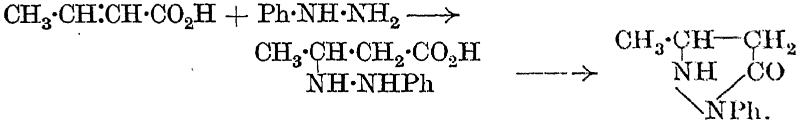
Preparation of β-Phenylaminobutyranilide, $Me\cdot CH(NHPh)\cdot CH_2\cdot CONHPh$.—Crotonic acid (8·6 g.) is heated for 4 hours at 180—190° with two molecular proportions of aniline (20 g.). The product is treated with ice and then hydrochloric acid. The solid, which separates, is the hydrochloride of the required amino-acid anilide. On decomposition with sodium bicarbonate in water the free amino-anilide is obtained, m. p. 93°.

Maleic and fumaric acid behave similarly toward aniline to give the anil of phenylasparagine (Tingle and Bates, *J. Amer. Chem. Soc.*, 1909, **31**, 1233).

Hydroxylamine reacts comparatively easily with some αβ-unsaturated acids, as for example with cinnamic acid.

Preparation of β-Hydroxyamino-β-phenylpropionic Acid.—An alcoholic solution of hydroxylamine (2 mol. props.) is poured on cinnamic acid and the paste thus obtained is heated for 2 hours. The β-hydroxyamino-acid separates on cooling and is purified by crystallisation from hot alcohol, m. p. 165° (decomp.) after reddening at 154° (Posner, *Ber.*, 1903, **36**, 4308; compare *ibid.*, 1905, **38**, 2320; Posner and Oppermann, *ibid.*, 1906, **39**, 3706).

Phenylhydrazine behaves similarly, but with the important difference that elimination of the elements of water occurs between the carboxyl group and the hydrazine residue to give pyrazolidones :—



$$CH_3\cdot CH{:}CH\cdot CO_2H + Ph\cdot NH\cdot NH_2 \longrightarrow \underset{NH\cdot NHPh}{CH_3\cdot \underset{|}{C}H\cdot CH_2\cdot CO_2H} \longrightarrow$$

(Knorr and Duden, *Ber.*, 1892, **25**, 759; 1893, **26**, 103, 109).

αβ-Unsaturated ketones also combine additively with ammonia and aniline to give β-amino ketones and their derivatives (Tambor and Wildi, *Ber.*, 1898, **31**, 349; Sokoloff and Latschinoff, *ibid.*, 1874, **7**, 1384; Kohn, *Monatsh.*, 1904, **25**, 135).

For the addition of semicarbazide and hydroxylamine to the ethylenic linking in αβ-unsaturated ketones and aldehydes see Tiemann (*Ber.*, 1900, **33**, 562), v. Auwers (*Annalen*, 1920, **421**, 13; *Ber.*, 1921, **54**, 990), Harries and Jablonski (*Ber.*, 1898, **31**, 1371), Harries (*Annalen*, 1904, **330**, 200).

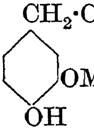
The presence of a second ethylenic bond in such a position that a conjugated system exists, $>C{:}\underset{|}{C}\cdot\underset{|}{C}{:}C<$, modifies the reactivity. Such systems are known to react abnormally with hydrogen and bromine giving products in which the addition takes place at carbon atoms 1 and 4 and the formation of a double bond between carbon atoms 2 and 3. This is illustrated by the following examples :—

$$CH_2{:}CH\cdot CH{:}CH_2 \xrightarrow{Br_2} CH_2Br\cdot CH{:}CH\cdot CH_2Br$$
$$CH_2{:}C(CH_3)\cdot CH{:}CH_2 \xrightarrow{Br_2} CH_2Br\cdot C(CH_3){:}CH\cdot CH_2Br$$
$$PhCH{:}CH\cdot CH{:}CHPh \xrightarrow{H_2} PhCH_2\cdot CH{:}CH\cdot CH_2Ph$$
$$CO_2H\cdot CH{:}CH\cdot CH{:}CH\cdot CO_2H \xrightarrow{H_2} CO_2H\cdot CH_2\cdot CH{:}CH\cdot CH_2\cdot CO_2H$$

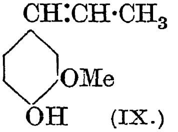
A number of similar types of addition have been described (Thiele, *Annalen*, 1899, **306**, 87, 145, 171, 176, 199, 201, 225; 1899, **308**, 333; 1900, **314**, 296; Willstätter, *ibid.*, 1901, **317**, 256). At one time this was thought to be a general reaction, but it now appears that the products of the addition do not all fall into line with this generalisation. Thus Chandrasena and Ingold (*J.*, 1922, **121**, 1310) pointed out that the presence of carbethoxyl or phenyl or an unsaturated grouping situated in the 1 or 4 or both positions resulted in the formation of 1 : 2- or 3 : 4-dibromides by the action of bromine (compare Hinrichsen, *Annalen*, 1904, **336**, 168; *Ber.*, 1904, **37**, 1121; Michael and Leighton, *J. pr. Chem.*, 1903, [ii], **68**, 521). More recently, Burton and Ingold have examined the products formed by addition to conjugated systems. They find that in the reduction by nascent hydrogen, both 1 : 2 and 1 : 4 addition take place and they have been able to indicate general rules governing such additions (*J.*, 1928, 904; 1929, 2022).

10. *Isomerisation of Unsaturated Compounds.*

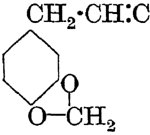
The position of the double bond in some unsaturated compounds may be changed by treatment with the appropriate reagent under suitable conditions. Allylbenzene and allyl phenyl ethers are very sensitive to warm alkali. On boiling for 5—10 minutes with potash lime they are converted into the isomeric propenyl derivatives (Claisen, *J. pr. Chem.*, 1922, [ii], **105**, 83). This is frequently employed to effect this change. It is, moreover, an isomerisation of industrial importance, for by means of it eugenol (VIII) and safrol (X) are converted into the corresponding *iso*-compounds (IX) and (XI) :—



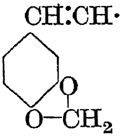
(VIII.)



(IX.)



(X.)



(XI.)

More recently Straus and Lemmel (*Ber.*, 1921, **54**, 25) have shown that Δ^2-dihydronaphthalene is transformed into Δ^1-dihydronaphthalene by the prolonged action of sodium ethoxide at 140°.

Ipatieff (*Ber.*, 1903, **36**, 2003) found that γ-methyl-Δ^α-butene, $Me_2CH·CH{:}CH_2$, is partly isomerised to γ-methyl-Δ^β-butene, $Me_2C{:}CHMe$, by passing over alumina at 525—535°. Similar methods—namely, passing the olefin over heated alumina or aluminium sulphate—have been used to isomerise the olefins (compare Gillet, *Bull. Soc. chim. Belg.*, 1920, **29**, 192; 1921, **30**, 138). It is possible that some similar isomerisation may account for the anomalous formation of olefins in the dehydration of the higher alcohols (compare Young and Lucas, *J. Amer. Chem. Soc.*, 1930, **52**, 1964).

The shifting of the double bond in $\alpha\beta$- and $\beta\gamma$-unsaturated acids under the influence of suitable catalysts is a well-known reaction (Fittig, *Annalen*, 1894, **283**, 51; *Ber.*, 1894, **27**, 2676). The reagents

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generally used to bring about the change are aqueous alkali, sodium alkoxides, sodium carbonate, ammonia, aliphatic amines, and piperidine. βγ-Unsaturated ketones behave similarly, but usually acid reagents are employed to effect the isomerisation.

These changes have recently been studied by Kon, Linstead, and their co-workers. They find that there is an equilibrium between the αβ- and βγ-forms using either potassium hydroxide or sodium ethoxide as catalysts.

$$\text{—CH:CH·CH}_2\text{·CO·R} \rightleftarrows \text{—CH}_2\text{·CH:CH·CO·R}$$

The probable mechanism of the change is also discussed (Linstead, *J.*, 1927, 362; Kon and Linstead, *ibid.*, 1929, 1269; Dickins, Hugh, and Kon, *ibid.*, p. 572; Farrow and Kon, *ibid.*, 1926, 2131; Goldberg and Linstead, *ibid.*, 1928, 2343; Eccot and Linstead, *ibid.*, 1930, 905).

(3) *Acetylenes.*

A characteristic reaction of acetylene and its mono-alkyl and aryl derivatives of the type R·C:CH is the formation of sparingly soluble silver derivatives by reaction with ammoniacal silver nitrate. Even more sensitive is the action of alcoholic nitrate, which can be used to detect quite small amounts of acetylenes, and for the higher acetylenes this is a more trustworthy reagent (Béhal, *Ann. Chim.*, 1888, [vi], **15**, 429; 1889, [vi], **16**, 200).

Ammoniacal cuprous chloride reacts similarly with monosubstituted acetylenes to give sparingly soluble reddish-yellow cuprous salts of the type R·C:C·Cu (Berthelot, *Annalen*, 1866, **138**, 245; **139**, 150). This reaction, like that with silver nitrate, appears to be characteristic of the grouping —C:CH, for it is also given by aldehydes, alcohols, and esters containing such a grouping.

A number of other metal derivatives have been prepared, but from the point of view of syntheses the most important are the sodium derivatives. These may be obtained by the action of metallic sodium on a cold ethereal solution of a mono-substituted acetylene (compare Lagermark, *Ber.*, 1879, **12**, 853) or by sodamide on acetylenes (Bourguel, *Compt. rend.*, 1924, **178**, 777; Meunier and Desparmet, *Bull. Soc. chim.*, 1924, [iv], **35**, 481; Picon, *Compt. rend.*, 1921, **173**, 155).

The disubstituted acetylenic hydrocarbons of the type R·C:C·Me or R·C:C·Et, which give no silver or cuprous salts, undergo rearrangement on heating in ether with sodium at about 100° to give the sodium salt of a mono-substituted acetylene. Thus methylethylacetylene, Me·C:C·Et, gives, under these conditions, the sodium salt of propylacetylene, $\text{C}_3\text{H}_7\text{·C:C·Na}$ (Favorski, *J. pr. Chem.*, 1888, [ii], **37**, 418; Gustavson and Demjanoff, *ibid.*, 1888, [ii], **38**, 206).

This change can also be brought about by heating with sodamide (Bourguel, *Compt. rend.*, 1924, **178**, 1984). The reverse change of a mono-substituted acetylene to one of the type R·C:C·Me can be achieved by heating with potassium hydroxide in alcohol at 170°.

Ethylacetylene, $\mathrm{Et{\cdot}C{\vdots}CH}$, yields dimethylacetylene, $\mathrm{Me{\cdot}C{\vdots}C{\cdot}Me}$, while propylacetylene, $\mathrm{Pr{\cdot}C{\vdots}CH}$, is converted into methylethylacetylene, $\mathrm{Et{\cdot}C{\vdots}C{\cdot}Me}$ (Favorski, *J. pr. Chem.*, 1888, [ii], **37**, 382). Apparently the type of alkyl group in the mono-substituted acetylene is an important factor, for, while acetylenes containing normal alkyl groups undergo this change, those containing a secondary alkyl group are isomerised to diolefins, *iso*propyl acetylene, $\mathrm{Me_2CH{\cdot}C{\vdots}CH}$, giving $\mathrm{Me_2C{:}C{:}CH_2}$. This isomerisation probably depends on the addition and subsequent elimination of the elements of alcohol, for from the product of the action of alcoholic potash on allylene, $\mathrm{Me{\cdot}C{\vdots}CH}$, Favorski has isolated $\mathrm{CH_2{:}C(OEt){\cdot}CH_3}$.

The alkali metal derivatives of the acetylenes are useful reagents for the introduction of the acetylenic group. Thus, monosodioacetylene in liquid ammonia reacts smoothly with primary alkyl iodides to give homologues of acetylene (Lebeau and Picon, *Compt. rend.*, 1913, **156**, 1077; Picon, *ibid.*, 1919, **168**, 894). Other reactions include the formation of acetylenic acids by the action of carbon dioxide or chloroformic esters (Glaser, *Annalen*, 1870, **154**, 140; Lagermark, *Ber.*, 1879, **12**, 853; Lagermark and Eltekoff, *ibid.*, p. 854; Favorski, *loc. cit.*); the formation of ketones by reaction of the sodium acetylenes with acyl chlorides (Nef, *Annalen*, 1888, **308**, 276); the production of acetylenic alcohols by the action of ketones on the sodium derivative (Nef, *loc. cit.*, p. 281; Moureu and Delange, *Compt. rend.*, 1901, **133**, 105; Moureu and Desmots, *ibid.*, 1901, **132**, 1223; 1902, **134**, 355; Hess and Munderloh, *Ber.*, 1918, **51**, 377). This reaction goes more smoothly and is stated to give better yields, if instead of the sodium derivative of the acetylene, the free hydrocarbon is allowed to react with the sodium derivative of the ketone (Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, **2**, 184; Wouseng, *Ann. chim.*, 1924, [x], **1**, 343).

By virtue of their unsaturated linkages the acetylenes are able to combine additively with hydrogen, halogens, halogen hydrides, hypochlorous acid, and similar substances under conditions somewhat similar to those obtaining for the olefins.

The combination with halogens can be considered as proceeding in two stages. First, the addition of 1 molecule of the halogen to form a disubstituted olefin, and if this substance can combine with a further molecule of halogen, the final product will be a tetrahalogen derivative of the type $\mathrm{R{\cdot}C(Hal)_2{\cdot}C(Hal)_2{\cdot}R'}$. From the considerations previously discussed it is obvious that the addition of 4 atoms of halogens depends more on the nature of the groups present in the acetylene than on the halogen used. Acetylene and its immediate homologues react readily with bromine and chlorine. The hydrocarbon must generally be diluted in order to moderate the reaction. Iodine also combines additively. On the other hand, diphenylacetylene, $\mathrm{Ph{\cdot}C{\vdots}C{\cdot}Ph}$, gives only the dibromide, although chlorine at low temperatures gives a tetrachloride. Acetylene dicarboxylic acid and phenylpropiolic acid also form the corresponding dibromides.

When the elements of water are added to the triple bond a product containing a carbonyl group results, in accordance with the following scheme:—

$$R{\cdot}C{:}C{\cdot}R + H_2O \longrightarrow R{\cdot}CO{\cdot}CH_2{\cdot}R.$$

With acetylene the product is acetaldehyde, but with its homologues only ketones result, the oxygen never becoming attached to the terminal carbon atom.

This hydration can be effected directly by heating the acetylenic hydrocarbon with water to about 300° (Degrez, *Ann. Chim.*, 1894, [vii], **3**, 209). A more convenient method for many acetylenes, as tolane, $Ph{\cdot}C{:}C{\cdot}Ph$, or caprylidine, $C_6H_{13}C{:}CH$, consists in dissolving the hydrocarbon in concentrated sulphuric acid and subsequently diluting with water (Béhal, *Bull. Soc. chim.*, 1887, **47**, 33). This method succeeds also with some of the acetylenic acids; thus phenylpropiolic ester gives benzoylacetic ester (Baeyer and Perkin, *Ber.*, 1882, **15**, 2705; compare Holt and Baruch, *ibid.*, 1893, **26**, 838). Many of those acetylenic acids which do not give good yields of ketones by this method do so on prolonged heating with alcoholic potash (Moureu and Delange, *Compt. rend.*, 1901, **132**, 1121; 1903, **136**, 753).

Mercuric salts in presence of aqueous acids facilitate the hydration of acetylene to acetaldehyde in a remarkable way. This process has been the subject of many investigations. It is one of considerable technical importance, in that the acetaldehyde can be directly converted by oxygen under suitable conditions to anhydrous acetic acid, or by the action of small amounts of aluminium ethoxide into ethyl acetate (see p. 161). The process for the conversion of acetylene into acetaldehyde consists essentially in passing acetylene into an aqueous solution of an acid containing a mercury salt. The many patents covering this reaction differ chiefly in the concentration of the acid, the temperature at which the reaction is effected, and in the methods of removing the acetaldehyde. A laboratory method has been described by Neumann and Schneider (*Z. angew. Chem.*, 1920, **33**, 189); they state that the best conditions for the conversion of acetylene to acetaldehyde consist in passing acetylene into 96% acetic acid containing 3% of mercuric sulphate and maintained at 30°.

The action of the mercury salt is apparently connected with the formation of an additive compound. The best defined of these has the composition $C_2H_2,HgCl_2$, and results by passing acetylene into an alcoholic or aqueous solution of mercuric chloride under suitable conditions (Biginelli, *Ann. Farm. Chim.*, 1898, 16; Brame, *J.*, 1905, **87**, 427; Chapman and Jenkins, *ibid.*, 1919, **115**, 847). Somewhat similar addition compounds result, although of not so well defined composition, if aqueous solutions of other mercuric salts are used (Nieuwland and Maguire, *J. Amer. Chem. Soc.*, 1906, **28**, 1025; K. A. Hofmann, *Ber.*, 1905, **38**, 1999).

CHAPTER II

HYDROCARBONS (*continued*)

(II) AROMATIC HYDROCARBONS

(1) Benzene and its Homologues.
  1. Oxidation.
  2. Additive Reactions.
  3. Substitution.
    (*a*) Nitration.
    (*b*) Sulphonation.
    (*c*) Halogenation.
    (*d*) Friedel and Crafts Reaction.
      1. Formation of Hydrocarbons.
      2. Formation of Ketones.
      3. Formation of Aldehydes.
      4. Formation of Acids and Amides.
    (*e*) Introduction of other Substituents.
    (*f*) Stability of Substituents in the Benzene Nucleus.
(2) Polycyclic Aromatic Hydrocarbons.
  1. Additive Reactions.
  2. Oxidation.
  3. Substitution.
    (*a*) Naphthalene.
    (*b*) Anthracene.
    (*c*) Acenaphthene.
    (*d*) Phenanthrene.

(1) *Benzene and its Homologues.*

1. *Oxidation.*

IN spite of formulation with unsaturated valencies, the nucleus of the aromatic hydrocarbons is comparatively stable to oxidation. Benzene is attacked only slowly by aqueous permanganate, or by an aqueous solution of chromic acid. This comparative stability of the aromatic nucleus is further illustrated by the behaviour of the alkylbenzenes. On oxidation the side-chain is attacked preferentially, producing carbonyl derivatives and carboxyl derivatives of benzene, the type of product being dependent on the experimental conditions. In general, the action of alkaline permanganate or of chromic acid yields acids, while manganese dioxide and sulphuric acid produces carbonyl compounds.

The oxidation of side-chains in the aromatic nucleus to carboxyl groups is important in that it can be applied to nitro and halogen nuclear-substituted homologues of benzene, and with suitable precautions to even aminoalkylbenzenes. Such oxidations accordingly serve not only to prepare substituted benzoic acids, but also to establish the orientation of alkyl groups in any substance of unknown configuration, by referring them to substituted benzoic acids of known orientation.

Oxidation by permanganate is affected generally by heating the substance under reflux with an aqueous solution of permanganate (about 2—5% solution) containing sodium carbonate. The process is described in detail below.

When more than one alkyl group is present, it is possible to effect the oxidation in stages, by using the necessary amount of permanganate for the oxidation of one or two alkyl groups. When the alkyl groups are different, one may suffer oxidation preferentially, as in cymene, where the methyl group is oxidised first with the formation of *p*-*iso*propylbenzoic acid.

Alkyl groups attached to the benzene nucleus may be oxidised to carboxyl by the use of chromium trioxide in moderately concentrated sulphuric acid. The use of this reagent is usually confined to *meta*- and *para*-compounds, for *ortho*-derivatives, if they are affected at all by this reagent, are usually broken down to non-aromatic compounds.

Diluted nitric acid has been extensively used for the oxidation of side-chains. It has, however, the disadvantage that the product usually contains appreciable amounts of nitro-compounds. It has been used advantageously in presence of dissolved permanganate for the oxidation of tetrahalogen-substituted xylenes to the corresponding phthalic acids.

✓ *Oxidation of* p-*Chlorotoluene to* p-*Chlorobenzoic Acid.*—A saturated solution of permanganate is added gradually to *p*-chlorotoluene heated under reflux in a brine bath. When no more permanganate is reduced and there remains no unchanged chloro-compound, the reaction mixture is saturated with sulphur dioxide till all the suspended manganese dioxide has dissolved. *p*-Chlorobenzoic acid separates on cooling, m. p. 235—236°.

✓ *Oxidation of* p-*Nitrotoluene to* p-*Nitrobenzoic Acid.*—A mixture of *p*-nitrotoluene (23 g.), crystallised sodium dichromate (68 g.), and water (150 c.c.) is stirred mechanically in a flask fitted with a reflux condenser, while 200 g. of concentrated sulphuric acid are added gradually from a tap funnel. The mixture is then gently heated on a gauze for about ½ hour, then cooled and mixed with 200 c.c. of water. The precipitate of crude *p*-nitrobenzoic acid is collected on a pad of glass wool and washed with about 100 c.c. of water. The crude acid, which is dark coloured, is freed from admixed chromium compounds by digesting with 100 c.c. of *N*-sulphuric acid on a water-bath. The residue, after washing with water, is triturated in a mortar with water and the resulting paste warmed with 5% aqueous sodium hydroxide solution. The insoluble matter is collected by filtration. The filtrate yields *p*-nitrobenzoic acid on acidifying. It is purified by crystallisation from benzene, m. p. 237—238°—yield about 20—23 g.

Oxidation of 2 : 4 : 6-*Trinitrotoluene* to 2 : 4 : 6-*Trinitrobenzoic Acid.*—Trinitrotoluene (36 g.) is mixed with concentrated sulphuric acid (360 g.) and stirred mechanically while powdered sodium dichromate (54 g.) is added gradually. The temperature of the reaction mixture must be kept at 45—55° during the oxidation. The stirring is continued for 2 hours after all the oxidising agent has been added, when the mixture is poured on 400 g. of crushed ice. The crude trinitrobenzoic acid is filtered and washed with water till free from acid.

It is purified by stirring a suspension of the crude acid in 200 c.c. of water while dilute aqueous sodium hydroxide is added drop by drop till a faint red colour is produced, which persists for about 5 minutes. The solution is then filtered from unchanged trinitrotoluene, after discharging the colour with a few drops of acetic acid. Pure trinitrobenzoic acid separates from the filtrate on adding a slight excess of 50% sulphuric acid—yield 23—25 g. (Clarke and Hartman, *Organic Syntheses*, 1922, **2**, 95).

✓ The side-chain may also be oxidised to $-CHO$ or $-CO{\cdot}R$ by the application of the appropriate methods. The use of chromyl chloride results in the formation of $-CHO$ from methyl groups. Hydrocarbons with longer side-chains are converted into a mixture of ketone and aldehyde. For example, ethylbenzene gives a mixture of acetophenone and benzaldehyde, while propylbenzene gives benzyl methyl ketone as the principal product (v. Miller and Rohde, *Ber.*, 1890, **23**, 1070). This method of oxidation was introduced by Etard (*Compt. rend.*, 1877, **84**, 127; *Ann. Chim.*, 1881, [iv], **22**, 218), and from many methylbenzenes gives good yields of the corresponding aldehydes. It is, however, necessary to take special precautions, as the reaction may become very vigorous.

Preparation of p-*Tolylaldehyde.*—*p*-Xylene (45 g.) diluted with twice its volume of chloroform is added slowly, over a period of 1½ hours, to 150 g. of chromyl chloride in 200 c.c. of chloroform. The reaction is controlled by cooling in a bath of ice. The reaction mixture is stirred during the addition of the xylene and for ½ hour after all the hydrocarbon has been added. It is kept over-night and then transferred to a round-bottomed flask containing a little water. An aqueous solution of sulphurous acid is added till all the chromic acid has been reduced. The product is then steam distilled. The chloroform layer is separated from the distillate, evaporated, and the residual aldehyde purified through its bisulphite compound—yield 70—80% (Law and F. M. Perkin, *J.*, 1907, **91**, 261).

✓ A number of other methods have been described for the preparation of aldehydes from alkylbenzenes; oxidation with manganese dioxide and diluted sulphuric acid (Fournier, *Compt. rend.*, 1901, **133**, 634), with persulphate and silver sulphate, with lead peroxide and sulphuric acid, or electrolytic oxidation. A comparison of the effectiveness of these processes has been made by Law and Perkin (*loc. cit.*). An interesting method of preparation from methylbenzenes has been described by Thiele and Winter (*Annalen*, 1900, **311**, 353). The hydrocarbon is oxidised by chromic acid in acetic anhydride containing sulphuric acid, and the aldehyde is converted into its diacetate, which protects it from further oxidation.

Preparation of p-*Nitrobenzaldehyde Diacetate.*—*p*-Nitrotoluene (5 g.) is dissolved in a mixture of acetic anhydride (40 g.), 15 g. of sulphuric acid, and 40 g. of glacial acetic acid. The mixture is cooled in ice, and solid chromic oxide (10 g.) added gradually with vigorous mechanical stirring. The temperature is maintained between 0 and 10° throughout the reaction. The product is precipitated by pouring on ice, and after washing with water, is purified by crystallisation from alcohol. *p*-Nitrobenzaldehyde diacetate is obtained as prisms, m. p. 125°. It is hydrolysed to *p*-nitrobenzaldehyde by heating with dilute acid.

Oxidation of aromatic hydrocarbons containing $-H_2C{\cdot}C_6H_5$ as a side-chain proceeds smoothly by the action of chromic acid mixture or chromic acid in glacial acetic acid, with the formation of a diaryl ketone. Halogen and nitro-nuclear-substituted diphenylmethanes react similarly, but compounds such as tolylphenylmethane or xylylphenylmethane have the methyl groups oxidised with the simultaneous formation of benzophenone carboxylic acids.

2. *Additive Reactions.*

Although the nucleus of aromatic hydrocarbons is comparatively stable to oxidation, it can be reduced fairly readily, giving *cyclo*hexane or a homologue as the final product. The most convenient methods of reduction depend on the use of hydrogen in presence of a suitable catalyst, either by the Sabatier–Senderens process, or the Willstätter method.

In the former process the vaporised hydrocarbon mixed with hydrogen is passed over reduced nickel at 180—200°. The experimental conditions depend largely on the hydrocarbon used; those with long side-chains tend to eliminate the alkyl group at above 200°. The preparation of the catalyst also appears to exert an influence on the rate of reduction, and also on the reverse process of dehydrogenation, which normally takes place at higher temperatures (compare Skita and Ritter, *Ber.*, 1911, **44**, 668). For the experimental details of this method, the original papers of Sabatier and Senderens should be consulted (*Compt. rend.*, 1901, **132**, 210, 566, 1254; see also Sabatier, *La Catalyse*). On the preparation of the catalyst see also papers by Pfaff and Brunck (*Ber.*, 1923, **56**, 2463); Zelinski and Kommarevski (*ibid.*, 1924, **57**, 667). This process can also be employed for the reduction of phenols and amines (Sabatier and Senderens, *Compt. rend.*, 1903, **137**, 1025; Sabatier and Mailhe, *ibid.*, 1905, **140**, 350; Vavon and Detrie, *ibid.*, 1921, **172**, 1231; Schrauth, Wege, and Danner, *Ber.*, 1923, **56**, 260).

Another method of reduction involves the use of hydrogen in conjunction with platinum- or palladium-black or platinised asbestos (Willstätter and Hatt, *Ber.*, 1912, **45**, 1471; Wieland, *ibid.*, 1912, **45**, 2615; Skita and W. A. Mayer, *ibid.*, 1912, **45**, 3593; see p. 8).

Not only are the aromatic hydrocarbons able to attach six atoms of hydrogen, but benzene can combine additively, under suitable conditions, with chlorine and bromine, giving compounds of the type $C_6H_6X_6$. The addition of the halogen to benzene is favoured by sunlight, a condition first observed by Faraday (*Phil. Trans.*, 1825, 440; compare Mitscherlich, *Annalen*, 1835, **16**, 172), who also isolated a crystalline solid from the reaction. This was shown by later investigators to be a mixture of two stereoisomeric hexachloro*cyclo*hexanes, $C_6H_6Cl_6$ (Matthews, *J.*, 1891, **59**, 165; 1892, **61**, 110; 1898, **73**, 243). Bromine behaves similarly giving a hexabromide. Both the hexahalogen compounds are decomposed by the action of hot alkaline solutions to give 1 : 2 : 4-trihalogen-substituted benzenes. The alkylbenzenes, under the conditions which favour the production of hexachloro*cyclo*hexane from benzene, are substituted in the side-chain.

Additive compounds are formed also by the action of ozone and of hypochlorous acid on benzene (Carius, *Annalen*, 1865, **136**, 324; Harries and Weiss, *Ber.*, 1904, **37**, 3431).

A further manifestation of the property of these hydrocarbons to combine additively is the formation of double compounds with some polynitro-compounds and with quinones. Thus a warm solution of picric acid in benzene deposits crystals of benzene picrate on cooling; it is, however, unstable, and loses benzene on exposure to the air (Fritsche, *J. pr. Chem.*, 1858, (1), **73**, 282). The picrates of some of the higher homologues are more stable, those of 1 : 2 : 3 : 4-tetramethylbenzene and pentamethylbenzene being stable enough to be recrystallised from alcohol (Töhl, *Ber.*, 1888, **21**, 905; Jacobsen, *ibid.*, 1887, **20**, 898). 1 : 3 : 5-Trinitrobenzene also forms double compounds with benzene and its homologues, that derived from benzene being unstable, but those from durene and hexamethylbenzene can be crystallised from acetic acid (Pfeiffer, *Annalen*, 1916, **412**, 298). Quinones, and more especially the tetrahalogen-substituted *p*-benzoquinones, also give addition compounds with aromatic hydrocarbons (Pfeiffer, *ibid.*, 1916, **412**, 291).

3. *Substitution.*

The usual action of reagents on benzene and its homologues is the replacement of one or more hydrogens in the nucleus. Thus nitric acid reacts to give nitro-compounds; sulphuric acid to give sulphonic acids. Halogens, alkyl, acyl, aldehyde groups and many others can also be introduced into the aromatic nucleus by suitable methods.

(a) *Nitration.*—The substitution of hydrogen in the aromatic nucleus by nitro-groups is achieved by the action of concentrated nitric acid. In this reaction it is necessary to prevent undue dilution of the nitric acid by the water liberated, either by employing a moderate excess of fuming nitric acid or by using a mixture of concentrated nitric acid with concentrated sulphuric acid. This latter method is generally the more convenient, for if slightly more than one molecular proportion of nitric acid diluted with concentrated sulphuric acid be used, benzene and its immediate homologues yield mononitro-compounds smoothly. Two or three groups can be introduced by the use of a greater proportion of nitrating mixture at higher temperatures. The use of the nitrating mixture of nitric acid and sulphuric acid is best illustrated by typical examples.

Preparation of o- *and* p-*Nitrotoluenes.*—A well-cooled mixture of 20 g. of nitric acid (*d*, 1·42) and of 30 g. concentrated sulphuric acid is dropped slowly into 20 g. of toluene. The mixture is stirred during the addition of the acid and the temperature is maintained at about 30° by suitable cooling. When all the acid has been added, the temperature is gradually raised to 50° and kept at this point for about 1 hour. It is then cooled, transferred to a separating funnel, and the lower layer of acid run off. The mixture of crude *o*- and *p*-nitrotoluenes is then washed successively with water, dilute sodium carbonate solution, and water. The product is a mixture of about 63% *ortho*, and about 35% *para*, the rest being *meta*. A small proportion of the *para* can be obtained by cooling the crude product in a freezing mixture of ice and salt. A better separation is achieved by distilling off about half of the mixture under reduced pressure. The residue consists largely of *para* which solidifies on cooling to 0°. The distillate is rich in *ortho*, and on cooling to − 15° the *ortho* separates out in a crystalline state. It can be purified by repeating the operations of distillation and freezing.

A similar process of nitration can be employed to obtain the nitroxylenes, nitrobenzene and also the nitrohalogenbenzenes.

Preparation of o- *and* p-*Nitrobromobenzenes.*—Bromobenzene (15 g.) is added slowly to a well-cooled and efficiently stirred mixture of 10 g. nitric acid (d, 1·42) and 15 c.c. of concentrated sulphuric acid. When all the bromobenzene has been added, the reaction is completed by allowing the temperature to rise to 30°. The mixture of nitro-compounds is isolated by pouring into water, and washing the collected precipitate till free from acid. Crystallisation from 50% aqueous alcohol yields almost pure *p*-nitrobromobenzene, m. p. 125°. The mother liquor contains the *ortho* isomeride contaminated by some *para.*

Dinitration and trinitration succeeds by the use of a larger proportion of mixed acid and usually a higher temperature.

Preparation of 2 : 4-*Dinitrotoluene.*—*p*-Nitrotoluene (50 g.) is added to a mixture of 20 g. nitric acid (d, 1·42) and 200 g. of concentrated sulphuric acid maintained at 40—50°. The mixture is gradually raised to 70° and kept at this temperature for 30 minutes. After cooling, it is cautiously diluted with 40 c.c. of water and the dinitro-compound separated off (W. H. Gibson, Duckham, and Fairbairn, *J.*, 1922, **121**, 278).

Preparation of 2 : 4 : 6-*Trinitrotoluene from* 4-*Nitrotoluene.*—100 G. of *p*-nitrotoluene are added to a mixture of 800 g. of concentrated sulphuric acid and 200 g. of nitric acid (85% concentration) maintained at 50°. The temperature is gradually raised to 120° during 5 hours. The product is isolated by pouring into an excess of ice water. The yield is 158 g. of practically pure trinitrotoluene.

It appears that the formation of di- and tri-nitro-compounds proceeds more readily with toluene and xylene than with benzene, for benzene yields a trinitro-compound only with difficulty. Indeed, the most convenient method of preparing trinitrobenzene is by the oxidation of trinitrotoluene, and subsequent decarboxylation of the trinitrobenzoic acid thus formed (see p. 208). Dinitrobenzene results by the action of hot fuming nitric acid on benzene. *o*-Xylene, on the other hand, is converted smoothly into dinitroxylenes by the action of an excess of fuming nitric acid at 25° (Crossley and Renouf, *J.*, 1909, **95**, 215). The dinitro-compound of mesitylene is formed by dropping the hydrocarbon into a moderate excess of fuming nitric acid cooled by a external bath of ice (Fittig, *Annalen*, 1867, **141**, 133). The preparation of mononitro-mesitylene is indeed a matter of some difficulty, and succeeds best by the use of glacial acetic acid as a diluent.

Preparation of Nitromesitylene.—50 G. of fuming nitric acid (*d*, 1·5) are added to a solution of 50 g. of mesitylene in 200 g. of glacial acetic acid and the mixture is heated for about an hour so that it just refluxes. It is then cooled and poured into half a litre of ice water. The precipitated oil is taken up in ether, the ethereal solution washed with water, and then three times with 30% potassium carbonate solution to remove mesitylenic acid. It is then washed three times with 10% sodium hydroxide solution to remove ω-nitromesitylene. The washed ethereal layer contains, in addition to nitromesitylene, unchanged hydrocarbon, and usually some resinous matter. After the evaporation of the solvent it is best purified by distillation in steam, when the resinous matter remains as a non-volatile mass. The oil which has distilled over with the steam is collected and fractionally distilled under reduced pressure. The yield of nitromesitylene, m. p. 41—42°, is approximately 10—20 g.

ω-Nitromesitylene is isolated from the sodium hydroxide washings by saturating with carbon dioxide and extracting with ether. A further amount is obtained from the carbonate washings by a similar process. It is purified by distillation in steam and is obtained as a solid, m. p. 47°. The solution remaining after the extraction of the ω-nitromesitylene yields mesitylenic acid on adding an excess of hydrochloric acid (G. Schultz, *Ber.*, 1884, **17**, 477; Bamberger and Rising, *ibid.*, 1900, **33**, 3625).

In contrast to mesitylene, its isomer ψ-cumene is comparatively difficult to nitrate. The mononitro-compound is best prepared by the action of mixed acid on ψ-cumene under carefully regulated conditions (Schultz, *Ber.*, 1909, **42**, 3606).

Preparation of 5-Nitro-ψ-Cumene.—A mixture of 35 g. of nitric acid (*d*, 1·51) and 52 g. of concentrated sulphuric acid is run slowly into 30 g. of ψ-cumene. The temperature of the nitration must not be allowed to rise above 20° and it must be stirred continuously. After 5 hours the nitration mixture is poured on to ice, and the semi-solid product, after taking up in ether and washing with sodium carbonate solution, is distilled in steam.

Further anomalies are encountered in the nitration of tetra- and penta-methylbenzenes. Thus, durene yields a dinitro-compound with nitric acid, and all attempts to prepare a mononitro-compound by direct nitration have failed (Cain, *Ber.*, 1895, **28**, 967; Rügheimer and Hankel, *ibid.*, 1896, **29**, 2171; Willstätter and Kubli, *ibid.*, 1909, **42**, 4151). Pentamethylbenzene, which gives no nitro-compound by the usual methods, loses a methyl group when treated in chloroform solution with absolute nitric acid and sulphuric acid, and yields 1 : 2 : 3 : 4-tetramethyl-5 : 6-dinitrobenzene (Willstätter and Kubli, *loc. cit.*).

Other nitrating agents employed for the production of nitro-hydrocarbons are anhydrous nitric acid in carbon tetrachloride or chloroform (Willstätter and Kubli, *loc. cit.*), acetyl nitrate (Pictet and Khotinski, *Ber.*, 1907, **40**, 1163), benzoyl nitrate (Francis, *J.*, 1906, **89**, 1; *Ber.*, 1906, **39**, 3798), inorganic nitrates such as copper nitrate or ferric nitrate in presence of acetic anhydride (Menke, *Rec. trav. chem.*, 1925, **44**, 141). Although benzoyl nitrate reacts normally with toluene, xylene, and mesitylene to give exclusively nuclear nitro-compounds, durene behaves differently. It is substituted exclusively in the side-chain by its action to give 2 : 4 : 5-trimethylphenylnitromethane. Pentamethylbenzene and hexamethylbenzene are also substituted in the side-chain (Willstätter and Kubli, *loc. cit.*).

If the nitration of benzene is effected by means of nitric acid and mercuric nitrate, nitrophenols are the principal products (Wolffenstein and Böters, *Ber.*, 1913, **46**, 586; Wolffenstein and Paar, *ibid.*, p. 589; Vignon, *Bull. Soc. chim.*, 1920 [iv], **27**, 547).

The introduction of nitro-groups into the side-chain of the lower homologues of benzene is effected by the use of dilute nitric acid. The alkylbenzene is heated in a sealed tube with dilute nitric acid (*d*, 1·12—1·01) at about 100—101° for 5—10 hours (Konovaloff, *Ber.*, 1895, **28**, 1860). Toluene under these conditions gives phenylnitromethane—the yield being under the most favourable conditions about 50%; ethylbenzene under similar conditions furnishes α-nitroethylbenzene. This method is similar to that employed for the production of nitro-paraffins (see p. 2).

For discussions on the probable mechanism of nitration see Wieland and Sakellarios (*Ber.*, 1920, **53**, 203), Wieland and Rahn (*ibid.*, 1921, **54**, 1770), Hollemann (*Die direkte Einführing v. Substituenten in den Benzolkern*, p. 476).

(b) *Sulphonation.*—Benzene and its homologues are converted into sulphonic acids by the action of fuming sulphuric acid at room temperature or by warming with concentrated sulphuric acid :—

$$C_6H_6 + H_2SO_4 \longrightarrow C_6H_5{\cdot}SO_3H + H_2O$$

A number of modifications of this process have been proposed, mainly for technical purposes. Thus, the mixture of the hydrocarbon and concentrated sulphuric acid may be mixed with kieselguhr to form a paste and the sulphonation completed by keeping the mixture for about 24 hours at room temperature (D.R.-P. 71,556). The sulphonation may also be achieved by heating with sulphuric acid containing a large proportion of sodium bisulphate (D.R.-P. 113,784).

The sulphonic acid is usually isolated as a salt, by neutralising the sulphonation mixture, which has been diluted with water, with carbonates of calcium, barium, strontium, or lead in order to precipitate the excess of sulphuric acid as sparingly soluble sulphate (the corresponding salts of the sulphonic acids are generally soluble in water). An alternative method is to pour the sulphonation mixture into a solution of sodium sulphate or a similar salt of the alkali metals, when the alkali salt of the sulphonic acid is usually precipitated. Not infrequently, the sulphonic acid may be obtained directly in a crystalline state by cautiously diluting the sulphonation mixture with water. An ingenious method for the direct production of crystalline sulphonic acid consists in heating the sulphuric acid with an excess of the hydrocarbon so that the water produced in the reaction distils away with the excess of hydrocarbon. The water is then separated mechanically and the hydrocarbon returned to the sulphonation mixture (H. Meyer, *Annalen*, 1923, **433**, 327).

Preparation of the Sodium Salt of Benzenesulphonic Acid.—A mixture of equal volumes of benzene and concentrated sulphuric acid is heated under reflux on a sand-bath and stirred mechanically till the benzene layer has disappeared. The reaction mixture is then poured into a large volume of cold water and neutralised by the addition of an aqueous paste of calcium carbonate after the solution has been heated. The neutralised mixture is boiled and filtered from the suspended calcium salts. The filtrate is then concentrated and treated with the exact amount of sodium carbonate dissolved in water. The precipitate of calcium carbonate is collected. Evaporation of the filtrate furnishes the sodium salt of benzenesulphonic acid.

Preparation of Mesitylenesulphonic Acid.—Mesitylene (100 c.c.) is vigorously shaken with concentrated sulphuric acid (200 c.c.) in a 500-c.c. flask fitted with an air condenser. The temperature rises rapidly to 60° and the solution of the hydrocarbon is complete in about 10 minutes. The clear yellowish liquid thus obtained is poured, while still warm, into 400 c.c. of concentrated hydrochloric acid kept at 10° and vigorously stirred. The sulphonic acid is precipitated. It is collected by filtration and drained by suction—yield 150 g. It is almost pure. It may be obtained quite pure by crystallisation from 600 g. of chloroform, m. p. 78° (L. I. Smith and Cass, *J. Amer. Chem. Soc.*, 1932, **54**, 1606).

Preparation of p-*Toluenesulphonic Acid.*—A mixture of 40 c.c. of concentrated sulphuric acid and 200 c.c. of toluene is boiled under reflux in an apparatus represented diagrammatically in Fig. 2. The heating is continued for about 5 hours, when nearly 18 c.c. of water should have been collected in the trap. The unchanged toluene is then distilled off. The residue solidifies to a mass of the monohydrate of *p*-toluenesulphonic acid by the addition of 12·5 c.c. of water. The product is drained on a porous tile and then recrystallised from a small amount of water, m. p. 92°—yield of crude product, 92 g. (H. Meyer, *loc. cit.*).

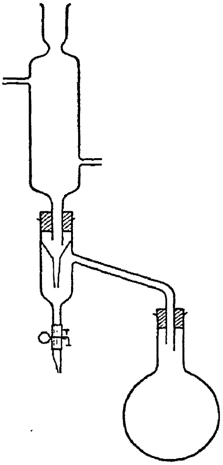

FIG. 2.

The immediate homologues of benzene, such as toluene, the xylenes, mesitylene, and ψ-cumene, are sulphonated more readily than benzene. The behaviour of durene and pentamethylbenzene towards sulphuric acid is abnormal. Thus pentamethylbenzene is converted into a mixture of hexamethylbenzene and 1 : 2 : 3 : 4-tetramethylbenzenesulphonic acid on keeping in contact with sulphuric acid at room temperature. Durene similarly furnishes a mixture of pentamethylbenzene and a mixture of two isomeric trimethylbenzenesulphonic acids (Jacobsen, *Ber.*, 1886, **19**, 1209 ; 1887, **20**, 896 ; 1888, **21**, 2814 ; L. I. Smith and Lux, *J. Amer. Chem. Soc.*, 1929, **51**, 2994 ; L. I. Smith and Cass, *ibid.*, 1932, **54**, 1614). Other examples of the abnormal action of concentrated sulphuric acid have been recorded. Monochlorodurene, on warming to 60° with sulphuric acid, gives chloropentamethylbenzene and ψ-cumenesulphonic acid (Töhl, *Ber.*, 1892, **25**, 1523). The action of sulphuric acid is not confined to the displacement of alkyl groups ; for monobromoprehnitene gives a mixture of prehnitene and dibromoprehnitene (Töhl, *loc. cit.*). Monobromo-ψ-cumene and monobromodurene exhibit similar reactions (Jacobsen, *Ber.*, 1887, **20**, 2837 ; 1889, **22**, 1581).

A second sulphonic group may be introduced by heating benzenesulphonic acid with concentrated sulphuric acid or oleum at temperatures between 200° and 250°. The principal product is benzene-*m*-disulphonic acid. A small amount of the isomeric *para*-acid is also formed. According to Polak (*Rec. trav. chim.*, 1910, [ii], **14**, 416) an equilibrium is reached if the treatment with sulphuric acid is continued. Rise in temperature and the presence of moisture accelerate the interconversion *meta*-acid ⇄ *para*-acid. The addition of catalysts, particularly mercuric sulphate, appears to favour the production of the *para*-acid (Behrend and Mertelsmann, *Annalen*, 1911, **378**, 352; compare, however, Holdermann, *Ber.*, 1906, **39**, 1250). An examination of the behaviour of toluenesulphonic acids in warm sulphuric acid has been made by Hollemann and Caland (*Ber.*, 1911, **44**, 2504). They find that *o*-toluenesulphonic acid and *p*-toluenesulphonic acid are interconvertible on heating with concentrated sulphuric acid, an equilibrium being reached. They conclude that the change *ortho* ⇄ *para* is an intramolecular reaction, and is not due to the elimination of the sulphonic group followed by resulphonation.

Chlorosulphonic acid may also be used for the preparation of sulphonic derivatives of the aromatic hydrocarbons. The arylsulphonic acid appears to be the first product of the reaction. By the action of an excess of chlorosulphonic acid on this, there results the chloride of the arylsulphonic acid (J. Stewart, *J.*, 1922, **121**, 2556; Harding, *ibid.*, 1921, **119**, 1261).

Preparation of o- *and* p-*Toluenesulphonyl Chlorides.*—100 G. of toluene are run slowly into 400 g. of chlorosulphonic acid cooled to 0°. The acid is stirred during the addition of the hydrocarbon and the temperature must be kept below 5°. The mixture is kept at this temperature for a period of 12 hours and then poured on ice. The toluenesulphonyl chlorides separate out. They are removed. Cooling to − 20° causes the *para* compound to crystallise, and it may be filtered off. The filtrate is rich in the *ortho* compound which may be obtained pure by fractional distillation under reduced pressure.

Preparation of 2 : 5-*Dichlorobenzenesulphonyl Chloride.*—*p*-Dichlorobenzene is added to 5-mol. proportions of chlorosulphonic acid and the mixture heated at 150° for 1 hour. After cooling, it is poured on crushed ice when the sulphonyl chloride separates as a solid, m. p. 39°.

Sulphonation is frequently employed for the separation of a mixture of two or more hydrocarbons, by taking advantage of differences in solubility of the sulphonic acids or of their derivatives. The hydrocarbons are recovered from the sulphonic acids by distillation in superheated steam or by heating with mineral acids at comparatively high temperatures. Frequently, separation is effected by taking advantage of the fact that sulphonic acids differ in the ease with which they are converted into the corresponding hydrocarbons. The following description illustrates this (compare also p. 44).

Separation of ψ-Cumene and Mesitylene.—Coal-tar solvent naphtha, b. p. 160—166°—free from basic and acidic impurities—is sulphonated by the process described already for mesitylene (p. 41).

The mixture of crude acids is suspended in 20% hydrochloric acid warmed to 30° and steam passed in. Mesitylene sulphonic acid is hydrolysed under these conditions. The solution after this treatment contains ψ-cumenesulphonic acid, from which the hydrocarbon is obtained by mixing with 50% sulphuric acid followed by distillation in steam (L. I. Smith and Cass, *J. Amer. Chem. Soc.*, 1932, **54**, 1614; compare Jacobsen, *Annalen*, 1877, **184**, 179; G. Schultz, *Ber.*, 1909, **42**, 3602).

(c) *Halogenation.*—The reaction of benzene and its homologues towards the halogens is determined by the conditions of temperature, the absence of catalysts, or the absence of light. Boiling benzene, or benzene exposed to sunlight, furnishes, by the action of chlorine or bromine, an additive compound $C_6H_6Hal_6$. Although it is not improbable that the alkylbenzenes may tend to form similar addition compounds, their reaction is complicated by the fact that these substances present to the halogen two points of attack, the nucleus and the side-chain.

The behaviour of the alkylbenzenes has been most thoroughly investigated for toluene. It has been established that in sunlight and in the absence of catalysts, toluene is chlorinated almost exclusively in the methyl group, giving successively benzyl halide, benzalchloride and finally benzotrichloride. If the toluene be heated, the reaction is similar. A combination of favourable conditions of sunlight and a hot hydrocarbon appears to be the best method of introducing halogen into the side-chain without in any way substituting the nucleus; and this holds not only for toluene, but also for the alkylbenzenes generally. (Hollemann and van Laan, *Proc. K. Akad. Wetensch. Amsterdam*, 1905, **8**, 512; Cohen, Dawson, Blockey, and Woodmansey, *J.*, 1910, **97**, 1623.)

Suitable catalysts, on the other hand, notably ferric chloride, iodine, or aluminium mercury couple, have the power of causing substitution to occur in the nucleus alone, even when other conditions favour halogenation of the side-chain.

Conditions can be arranged, therefore, so as to obtain either products halogenated exclusively in the nucleus or in the side-chain, and the examples given below serve to illustrate the two types of process.

For bromination or chlorination of the nucleus a number of suitable halogen carriers have been used. H. Müller (*J.*, 1862, **15**, 41) seems to have been the first to employ catalysts for this purpose. He showed that iodine and antimony pentachloride promoted very effectively the formation of chlorobenzenes by the action of the halogen on the hydrocarbon. Other available catalysts are iron filings or anhydrous ferric chloride, aluminium or aluminium chloride, aluminium–mercury couple, pyridine, molybdenum pentachloride. The general method of preparing the halogen nuclear-substituted aromatic hydrocarbons consists in adding to the hydrocarbon containing the catalyst the appropriate amount of bromine, or passing in chlorine until the desired increase in weight has been attained.

Preparation of o- *and* p-*Dichlorobenzenes.*—Chlorobenzene (15 g.) is saturated with chlorine, and the vessel and its contents are weighed. 0·2 G. of aluminium mercury couple * is added and the stream of chlorine continued until the increase in weight amounts to 4·6 g. The flask containing the chlorobenzene should be cooled during the chlorination. The product consists principally of a mixture of *o*- and *p*-dichlorobenzenes. It is freed from chlorine and hydrogen chloride by washing with water and sodium hydroxide solution, dried, and then cooled in a freezing mixture to remove the greater part of the *para* compound. The liquid portion separated from the crystalline *para* by filtration consists largely of the *ortho* with some dissolved *para* and trichlorobenzene. To separate the *ortho* from the *para*, advantage is taken of the resistance of *p*-dichlorobenzene to sulphonation. The liquid portion is treated with an equal volume of fuming sulphuric acid, and after keeping for an hour, it is diluted carefully by the addition of ice. The sulphonated product is now distilled in steam with the thermometer bulb in the liquid. A small amount of *p*-dichlorobenzene is collected while the temperature of the liquid is between 115° and 130°. Between 130° and 230°, the distillate contains 1 : 2 : 4-trichlorobenzene, but above 230° the decomposition of *o*-dichlorobenzene-sulphonic acid takes place and the distillate contains pure *o*-dichlorobenzene, which after separation from the distillate boils at 178° (yield 4 g.) (Cohen and P. Hartley, *J.*, 1904, **87**, 1362).

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* *Preparation of Al–Hg Couple.*—Clean strips of aluminium foil are covered by a saturated solution of mercuric chloride. The aqueous solution is poured off after about a minute, the aluminium washed successively with water, alcohol, and benzene. The couple, thus prepared, is used immediately.

Preparation of o- *and* p-*Chlorotoluenes.*—A stream of dry chlorine is led into toluene containing either 1% or 2% of its weight of iron wire or a small amount of iodine. When the increase in weight corresponds with the introduction of one atom of chlorine, the current of gas is stopped, the product freed from iron compounds and from chlorine. It consists principally of a mixture of *o*- and *p*-chlorotoluenes. The separation depends on the fact that the *para* is sulphonated more slowly than the *ortho*. The chlorination product is heated near its boiling point with two volumes of concentrated sulphuric acid. After cooling it is diluted with water, and the crude *para* separates out.

Preparation of 4 : 6-*Dibromo*-m-*xylene.*—160 G. of bromine (*i.e.* 5% excess over 4 mol. props.) are added gradually to 50 g. of *m*-xylene containing a small amount of iodine. After standing for 2 hours, the product, which has set to a paste of crystals, is stirred with sodium hydroxide solution to remove excess of bromine, washed with water, and pressed on a porous tile. It is finally purified by distillation under reduced pressure, b. p. 132°/12 mm., m. p. 69° (Auwers and Traun, *Ber.*, 1899, **32**, 3312). 2 : 5-Dibromo-*o*-xylene can be prepared similarly.

For the production of chlorinated benzenes, Silberrad (*J.*, 1922, **121**, **1015**) recommends the use of sulphuryl chloride in presence of aluminium chloride.

It is obvious that the absence of catalysts which promote nuclear halogenation is essential when the halogen is to be introduced into the side-chain. This side-chain substitution is promoted by the presence of sulphur or of phosphorus trichloride, although the halogenation can proceed quite smoothly in absence of these compounds (Häussermann and Beck, *Ber.*, 1892, **25**, 2445).

Preparation of o-*Methylbenzyl Bromide* (ω-bromo-*o*-xylene).—Bromine (252 g.) is added to 150 g. of *o*-xylene by means of a tap funnel, the stem of which extends below the surface of the hydrocarbon. The xylene is maintained at 130° by means of an oil-bath. When all the bromine has been added, the product is transferred to an evaporating dish and kept in a desiccator over potash till free from hydrogen bromide. It is then distilled at the ordinary pressure. ω-Bromo-*o*-xylene is collected at 215—218°, yield 80% of theory. The residue in the flask is *o*-xylylene dibromide (Atkinson and Thorpe, *J.*, 1907, **91**, 1695).

ω-Dibromo-*o*-xylene can be prepared similarly from 50 g. of *o*-xylene and 160 g. of bromine. The product on keeping in the desiccator solidifies, and after draining from oily impurities and crystallisation from chloroform is pure. Yield 85—90 g., m. p. 93° (W. H. Perkin, jun., *J.*, 1888, **53**, 5; Atkinson and Thorpe, *loc. cit.*).

The side-chain bromination of *m*- and *p*-xylenes can be accomplished similarly, but the product consists of a mixture of mono-, di-, and tri-bromoxylenes according to the relative amounts of bromine used. For particulars of the preparation of these compounds see Atkinson and Thorpe (*loc. cit.*).

The formation of iodo-substituted hydrocarbons, by the reaction of the hydrocarbon with elementary iodine, does not take place readily, and if the substitution is to proceed to any extent, it is necessary to remove the hydrogen iodide as fast as it is formed. To this end the iodination is carried out in presence of an oxidising agent, such as iodic acid, persulphate, or nitric acid or in presence of mercuric oxide. It is, however, more convenient to prepare the iodohydrocarbons through the diazo reaction if the amine necessary for such a reaction is readily accessible.

Preparation of Iodomesitylene.—Iodine (6 g.) and an equal weight of mesitylene are mixed in 25 g. of glacial acetic acid and a solution of 2 g. of iodic acid in 5 c.c. of water is added. The mixture is heated with vigorous stirring over a free flame for about 15 minutes. The addition of water precipitates crude iodomesitylene, which is freed from acid, and if necessary from iodine, by shaking with dilute sodium hydroxide solution. After drying, the oil is cooled in a freezing mixture, when iodomesitylene solidifies, m. p. 30°, b. p. 248—250° (Klages and Liecke, *J. pr. Chem.*, 1900, [ii], **61**, 311).

By a similar process, ethylbenzene, *p*-xylene, *m-tert.*-butyltoluene, and *iso*butylbenzene yield iodo-compounds (Klages and Storp, *ibid.*, 1902, [ii], **65**, 564). Benzene does not give any appreciable yield of iodobenzene under these conditions (Kekule, *Annalen*, 1866, **137**, 162). To bring about the reaction satisfactorily it is necessary to heat benzene with iodine and HIO_3 in a sealed tube at 200°.

The preparation of iodomesitylene and of iododurene can also be achieved by keeping a mixture of the appropriate hydrocarbon, mercuric oxide, and iodine at room temperature till the halogen has reacted. This may require several days (Töhl, *Ber.*, 1892, **25**, 1522).

The iodination of benzene and its homologues appears to go quite smoothly in presence of sodium persulphate and comparatively high yields of the iodo-substituted hydrocarbon are obtained by this method (Elbs and Jaroslavzev, *J. pr. Chem.*, 1913, [ii], **88**, 92).

Preparation of Iodobenzene.—A mixture of benzene (20 g.), iodine (20 g.), and sodium persulphate (80 g.) in 60 c.c. of glacial acetic acid is heated under reflux for about 15 hours. The product is isolated by dilution with water and separation of the oil. After the usual operations to free it from iodine and acid, it is distilled. The main product is iodobenzene, b. p. 184—186°, yield about 70% of theory. The residue consists of *p*-di-iodobenzene.

Toluene reacts under these conditions to give a mixture of *o*- and *p*-iodotoluenes; the *ortho* being present in greatest amount. From the xylenes and from *ψ*-cumene, iodo-derivatives can be similarly prepared.

Other methods for the direct introduction of iodine into the nucleus of aromatic hydrocarbons involve the use of iodine and concentrated nitric acid (Datta and Chatterjee, *J. Amer. Chem. Soc.*, 1917, **39**, 437; *Organic Syntheses*, 1929, **9**, 46), or iodine and sulphuric acid (Neumann, *Annalen*, 1887, **241**, 84), or iodine, sulphur, and moderately concentrated nitric acid (Edinger and P. Goldberg, *Ber.*, 1900, **33**, 2875).

(d) *Friedel and Crafts Reaction.*—Alkyl halides react with benzene in presence of $AlCl_3$ to yield alkylbenzenes. The reaction was first applied to the preparation of the homologues of benzene by Friedel and Crafts (*Compt. rend.*, 1877, **84**, 1392, 1450), but the scope of the reaction has since been enlarged to include the preparation of ketones, sulphones, aldehydes, amides, acid chlorides, etc.

1. *Hydrocarbon Synthesis.*—For a satisfactory reaction between the alkyl halide and the aromatic hydrocarbon the aluminium chloride must be anhydrous and the other reagents must be dry. The product may consist of mono-, di-, tri-, or even more complex alkylbenzenes according to the experimental conditions. When monoalkylbenzenes are required, it is usual, in order to prevent the undue formation of polyalkylbenzenes, to use an excess of the hydrocarbon, which also acts as a diluent in moderating the violence of the reaction.

The scope of the Friedel–Crafts reaction for the preparation of alkylbenzenes is restricted by the fact that those alkyl halides which are capable of isomerisation are generally isomerised during the condensation. Thus *n*-propyl halides give *iso*propylbenzenes, *n*-butyl halides give *sec.*-butyl derivatives, *iso*butyl halides give derivatives containing the *tert.*-butyl group. The tendency towards this isomerisation is apparently restricted by effecting the condensation at 0° (compare Heise, *Ber.*, 1891, **24**, 768), but even under these conditions the method is not satisfactory for the preparation of the higher *normal* alkylbenzenes. These can be obtained, however, quite conveniently by the Fittig reaction or by the reduction of the corresponding ketones, by Clemmensen's method.

A general method of carrying out the Friedel and Crafts synthesis has been developed by Bœdtker and his collaborators, and is exemplified by the following preparation (Bœdtker, *Bull. Soc. chim.*, 1901, [iii], **25**, 845).

Preparation of iso*Propylbenzene.*—A mixture of 100 g. of *n*-propyl chloride and 300 g. of benzene is dropped into a flask fitted with a reflux condenser and containing 700 g. of benzene and 20 g. of anhydrous aluminium chloride. The flask and its contents are maintained at about 80° by immersion in a bath of warm water. Access of moisture to the flask is prevented by fitting a suitable guard tube to the upper end of the condenser. When all the alkyl halide has been added, the reaction is allowed to continue until the evolution of hydrogen chloride almost ceases. Bœdtker recommends that the alkylation should be controlled by passing the evolved hydrogen chloride through a weighed flask containing water, the reaction being stopped when the theoretical amount of hydrogen chloride has been evolved.

The reaction mixture is finally poured on ice, the upper layer of hydrocarbon separated, and, after washing with dilute sodium hydroxide solution and water, is dried and fractionated. The yield of *iso*propylbenzene, b. p. 151—153°, is about 110—118 g.

The procedure can be used with other alkyl halides, even ethyl chloride. The yield of ethylbenzene from 100 g. of ethyl chloride under the conditions described is approximately 70—80 g. (Schreiner, *J. pr. Chem.*, 1910, [ii], **81**, 558). By the use of an excess of the appropriate alkyl halide several alkyl groups can be introduced.

The following papers should be consulted for experimental details: Jacobsen (*Ber.*, 1881, **14**, 2624), Galle (*ibid.*, 1883, **16**, 1745), L. I. Smith (*Organic Syntheses*, 1930, **10**, 32). The introduction of a second alkyl group into toluene by the Friedel–Crafts reaction appears to occur principally in the *meta* and *para* positions (Jacobsen, *loc. cit.*; Baur, *Ber.*, 1891, **24**, 2833; v. Auwers and Kolligs, *ibid.*, 1922, **55**, 3872), but the experimental evidence is not entirely satisfactory.

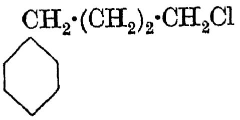
Halogen benzenes react similarly to benzene itself with alkyl halides giving *p*-alkylhalogenbenzenes (Bœdtker, *Bull. Soc. chim.*, 1906, [ii], **35**, 825). Nitro-compounds and phenols do not undergo this reaction.

Aluminium chloride may be replaced by anhydrous ferric chloride. Instead of using sublimed aluminium chloride as the catalyst, methods have been described in which the aluminium chloride is prepared *in situ*. This is effected either by the action of dry mercuric chloride on aluminium powder or filings in benzene suspension, or by passing a stream of hydrogen chloride into benzene containing aluminium filings (Radzievanovski, *Ber.*, 1895, **28**, 1137; Estreicher, *ibid.*, 1900, **33**, 439; Rây, *J.*, 1920, **117**, 1335).

Under suitable conditions aluminium chloride may also be used as a dealkylating agent. Hexamethylbenzene heated with anhydrous chloride gives methyl chloride and a mixture of penta-, tetra-, tri-, and di-methylbenzenes (Anschütz and Immendorff, *Ber.*, 1884, **17**, 2816; 1885, **18**, 657; Jacobsen, *ibid.*, 1885, **18**, 338; Anschütz, *Annalen*, 1886, **235**, 177). Apparently xylene is more resistant, for the yield of toluene from it is comparatively small (F. Fischer and Niggemann, *Ber.*, 1916, **49**, 1475; Bœdtker and Halse, *Bull. Soc. chim.*, 1916, [iv], **19**, 444; Copisarow, *J.*, 1921, **119**, 1806). This dealkylating action of aluminium chloride may be made use of for converting the residue of polyalkylbenzenes, remaining after a preparation of an alkylbenzene by the Friedel and Crafts method, into the required monoalkylbenzene, by diluting with benzene and heating under reflux with the addition of aluminium chloride (Radzievanovski, *Ber.*, 1894, **27**, 3235).

Halogen-substituted paraffins containing more than one halogen atom can also react with the aromatic nucleus under the influence of aluminium chloride yielding the corresponding aryl-substituted paraffin. Thus α : β-dibromoethane with benzene gives α : β-diphenylethane; chloroform furnishes triphenylmethane, while carbon tetrachloride gives as the end product triphenylmethyl chloride. This reaction does not appear to be convenient for introducing the benzyl group by the action of benzyl chloride. The action of $AlCl_3$ on some of the higher homologues of benzyl chloride is interesting. Thus δ-phenyl-α-chlorobutane (I) gives tetrahydronaphthalene (II); γ-phenyl-α-chloropropane (III) gives as the principal product a viscid oil of comparatively high molecular weight, but there is formed also a small amount of hydrindene (IV); ε-phenyl-α-chloropentane (V) gives a mixture containing a large proportion of phenyl*cyclo*pentane (VI) (v. Braun and Deutsch, *Ber.*, 1912, **45**, 1267).

γ-Phenyl-α-chlorobutane (VII), in contrast to its isomer, is scarcely affected by aluminium chloride (v. Braun, Grabowski, and Kirschbaum, *Ber.*, 1913, **46**, 1266). The behaviour of these chloro-compounds should be compared with that of the corresponding acid chlorides (pp. 49, 50).



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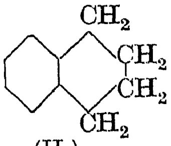

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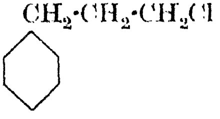

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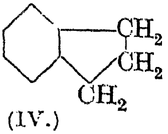

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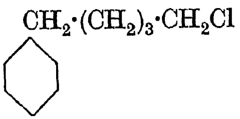

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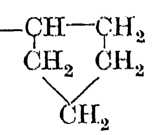

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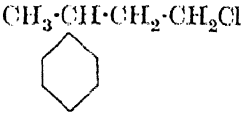


(VII.)

2. *The Formation of Ketones.*—In the presence of aluminium chloride, acyl chlorides react with the nucleus of the aromatic hydrocarbons and some of their derivatives to form ketones according to the equation,

$$C_6H_6 + R·CO·Cl \longrightarrow C_6H_5·CO·R + HCl.$$

While the hydrocarbon synthesis can be effected by the use of only a small proportion of aluminium chloride, the satisfactory production of ketones by this method requires, in general, at least one molecular proportion of aluminium chloride for every molecular proportion of the acid chloride.

The reaction succeeds not only with aromatic hydrocarbons, but also with their halogen-substituted derivatives, with phenol ethers, and even with aromatic amines in which the amino-group has been protected by acylation. Nitro-compounds and phenols do not yield ketones by this reaction, although there are one or two recorded instances of the introduction of acyl groups, after observing certain precautions, into phenols by the use of aluminium chloride.

A large variety of acyl chlorides can be employed in this condensation—the chlorides of the fatty acids and of the aromatic acids, carbonyl chloride, thiophosgene, sulphonyl chlorides, and the chlorides of dibasic acids. The chlorides of chloro-substituted fatty acids react entirely with the formation of chloro-substituted ketones of the type $C_6H_5·CO·CH_2Cl$.

The experimental conditions differ somewhat according to the nature of the compound into which it is desired to introduce the acyl residue. With aromatic hydrocarbons and their chloro-substituted derivatives it is usual to employ an excess to act as a diluent. When the amount of hydrocarbon is limited or it is solid, the reaction is carried out by using approximately molecular proportions of the reactants dissolved in carbon disulphide.

Preparation of p-*Tolyl Methyl Ketone.*—One kg. of toluene to which 160 g. of anhydrous aluminium chloride have been added is cooled in a bath of ice and 160 g. of acetyl chloride are run in gradually. At the same time precautions are taken to prevent access of moisture. When all the acyl chloride has been added, the reaction mixture is removed from the ice-bath, and allowed to warm to 20°. All reaction having ceased, the mixture is poured into water and acidified with dilute hydrochloric acid. The upper layer is removed, washed with water, dried, and the excess of toluene removed by distillation. The yield of ketone, b. p. 220° or 116°/23 mm., is about 162 g.

Preparation of ω-Chloroacetophenone.—Chloroacetyl chloride is dissolved in an excess of benzene and one molecular proportion of aluminium chloride added. A violent reaction ensues. When this has subsided, ice and hydrochloric acid are added. The benzene layer is separated, washed with water, dried, and the excess of benzene removed by distillation. The addition of light petroleum to the residue precipitates ω-chloroacetophenone in glistening plates, m. p. 59°. The yield is almost quantitative (Tutin, *J.*, 1910, **97**, 2500).

*Preparation of ω-Chloro-*o- *and* -p-*methoxyacetophenones.*—One molecular proportion of anisole is mixed with rather more than one equivalent of chloroacetyl chloride, and after diluting the mixture with three times its volume of carbon disulphide, one molecular proportion of powdered aluminium chloride is cautiously added. In order that the methyl group should not be split off, the flask and its contents should be kept quite cold during the addition of the aluminium chloride. After 3 hours, the carbon disulphide is decanted and the residue decomposed by the addition of ice and dilute hydrochloric acid. The product is extracted with ether, the ethereal solution washed with aqueous sodium hydroxide, dried, and the solvent evaporated. The residue on crystallisation from alcohol gives ω-chloro-*p*-methoxyacetophenone, m. p. 102°. The mother-liquors from the crystallisation of the *para*-compound contain a small amount of the *ortho* isomeride, which is separated mechanically and then crystallised several times. It separates in large diamond-shaped plates, m. p. 69° (Tutin, *loc. cit.*).

Hydroxy ketones can be prepared by heating an alkoxybenzene with an acyl chloride and aluminium chloride.

Preparation of ω-Chloro-4-hydroxyacetophenone.—Chloroacetyl chloride (12 g.) is added in one portion to a mixture of anisole (10 g.), carbon disulphide (50 g.), and anhydrous aluminium chloride (30 g.) previously heated under reflux on a steam-bath. The solvent is removed by distillation. The residue, after heating for 4 hours on a steam-bath, is decomposed by ice and dilute hydrochloric acid. The solid product is dissolved in the minimum volume of methyl alcohol and added in a thin stream to a 10% sodium carbonate solution (300 c.c.). The mixture is agitated for an hour, treated with charcoal, and acidified with hydrochloric acid. The ketone is then crystallised from 80% alcohol (yield, 7—8 g., m. p. 148°) (A. Robertson and Robinson, *J.*, 1928, 1464).

*Preparation of 4-Chlorophenyl-*n-*Propyl Ketone.*—*n*-Butyryl chloride (30 g.) is added gradually with continuous stirring to 83 g. of chlorobenzene mixed with freshly prepared aluminium chloride (35 g.). The temperature is maintained at 40—60°. After 4 hours, the product is poured on ice and the pale yellow oil, having been washed with aqueous sodium hydroxide solution, is distilled. 4-Chloro-*n*-propyl ketone is collected between 253° and 254° (uncorr.) as a colourless liquid which solidifies on cooling to a mass of tabular crystals, m. p. 36° (Morgan and Hickinbottom, *J.*, 1921, **119**, 1885).

The formation of hydrindone by the inner condensation of phenyl propionyl chloride is an interesting application of the Friedel and Crafts reaction (Kipping, *J.*, 1894, **65**, 480).

Preparation of a-Hydrindone.—Phenylpropionyl chloride (25 g.) is dissolved in light petroleum (60 c.c., b. p. 60—70°) and about 25 g. of anhydrous aluminium chloride are added. The mixture is warmed gently under reflux and shaken till it begins to boil. A lively evolution of hydrogen chloride sets in. When the evolution slackens the mixture is again warmed till the reaction becomes vigorous. The reaction is at an end when the evolution of hydrogen chloride ceases. The mixture is cooled, water added cautiously, and the hydrindone driven over in steam. The distillate is saturated with sodium sulphate and the petroleum layer separated. After washing the product with sodium carbonate solution and water, it is dried and the solvent removed, leaving hydrindone as an oil which solidifies on cooling to a mass of colourless crystals, m. p. 40—41°, yield 11 g. (Kipping, *loc. cit.*).

γ-Phenylbutyryl chloride and its derivatives containing alkyl groups in the side-chain similarly undergo internal condensation under the influence of aluminium chloride yielding ketotetrahydronaphthalene and its alkyl-substituted derivatives. This reaction is of importance in that it furnishes products which have been used in the synthesis of alkylnaphthalenes (Harvey, Heilbron, and D. G. Wilkinson, *J.*, 1930, 423; Heilbron and Wilkinson, *ibid.*, 1930, 2537; Wilkinson, *ibid.*, 1931, 1333).

The formation of ketones by the Friedel–Crafts reaction can be accomplished also by interaction of acid anhydrides with hydrocarbons and phenol ethers. The following general conditions for this condensation are given by Noller and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1892).

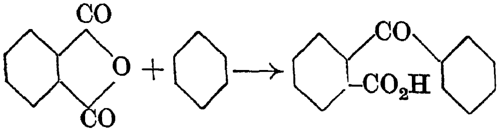
A solution of 0·5 mol. of aromatic hydrocarbon in 200 c.c. of carbon disulphide, in a 1-l. flask fitted with stirrer, dropping funnel and condenser, is mixed with 1·1 mol. proportions of powdered anhydrous aluminium chloride, and the appropriate acyl anhydride (0·5 mols.) added during 15 minutes. During this time the solvent boils and there is a rapid evolution of hydrogen chloride. When all the anhydride has been added the mixture is heated in a water-bath and stirred till there is practically no further evolution of hydrogen chloride. This usually requires about 30 minutes. The mixture is then cooled, poured on ice, and the solvent allowed to evaporate in a well-ventilated fume cupboard. The product is taken up in ether, the ethereal solution washed with water and dilute alkali, and concentrated after drying. The residual ketone is then distilled under reduced pressure.

When the hydrocarbon used in this condensation is available in quantity it may be used as the solvent in place of carbon disulphide.

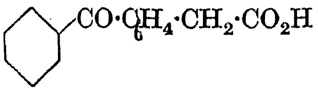
Acetophenone prepared in this way was obtained in good yield—76—83%, b. p. 201°.

This process can also be used for the preparation of ketones of phenol ethers.

The anhydrides of aromatic *o*-dibasic acids react with benzene in presence of aluminium chloride to furnish *o*-carboxylic acids of ketones. Thus phthalic anhydride and benzene yield *o*-benzoylbenzoic acid (VIII) (Friedel and Crafts, *Compt. rend.*, 1878, **36**, 1363; 1881, **92**, 833).



(VIII.)



(IX.)

Preparation of o-*Benzoylbenzoic Acid.*—Phthalic acid (50 g.) and benzene (175 g.) are mixed and 100 g. of sublimed aluminium chloride added. The mass is stirred mechanically. The anhydride soon dissolves and hydrogen chloride commences to be evolved. After about 2 hours, the temperature of the mixture is gradually raised by heating in an oil-bath till a temperature of 75° is reached after about 9 hours. The reaction is then complete. Water is gradually added to the mass and the benzene driven over by distillation in steam. The aqueous layer in the flask is poured off from the reaction mass, which is then treated with an excess of sodium carbonate solution. Steam is passed into this mixture for 4—5 hours, when the aluminium hydroxide is filtered off and benzoylbenzoic acid precipitated from the filtrate by the addition of hydrochloric acid—yield 71·5 g., m. p. 94° (Heller and Schülke, *Ber.*, 1908, **41**, 3627).

Substituted phthalic anhydrides behave similarly. If the proportion of aluminium chloride is reduced, the product contains a smaller or greater proportion of diphenylphthalide (Rubidge and Qua, *J. Amer. Chem. Soc.*, 1914, **36**, 732; Lawrance, *ibid.*, 1920, **42**, 1871; N. H. Stephens, *ibid.*, 1921, **43**, 1950; McMullen, *ibid.*, 1921, **43**, 1965).

Succinic anhydride condenses in a similar manner with benzene to yield β-benzoylpropionic acid (IX); with naphthalene to give a mixture of α- and β-naphthoylpropionic acids, and with phenanthrene (Haworth, *J.*, 1932, 1125; Haworth and Mavin, *ibid.*, 1933, 1012). These reactions have been used for providing material for the synthesis of phenanthrene, benzanthracene, and chrysene.

3. *Formation of Aldehydes.*—The introduction of the –CHO group into the nucleus of aromatic hydrocarbons can be accomplished directly by passing a stream of carbon monoxide and hydrogen chloride into the hydrocarbon to which have been added anhydrous aluminium chloride and some cuprous chloride. The dry gaseous mixture of carbon monoxide and hydrogen chloride appears to react in presence of aluminium chloride as if it were formyl chloride, H·COCl. Consequently this reaction can be considered as a special form of the ketone synthesis.

Preparation of m-*Xylylaldehyde.*—The apparatus required consists of a wide-necked flask or bottle fitted with a mechanical stirrer and inlet and exit tubes. In it are placed 30 g. of *m*-xylene, 45 g. of anhydrous aluminium chloride, and 4 g. of dry cuprous chloride. The mixture is maintained at about 40—50° by an external bath of warm water. A stream of dried hydrogen chloride and carbon monoxide is led through the stirred mixture until it becomes so viscous that the stirrer can be rotated with difficulty. This usually requires about 4—5 hours. The product is then treated with ice and distilled in steam. The distillate is taken up in ether, washed, dried, and fractionated. *m*-Xylylaldehyde passes over at 216—218° (yield 18 g.). The aldehyde may be purified further through its bisulphite compound.

For the best yields, it appears necessary for the volume of the carbon monoxide to be about twice that of the hydrogen chloride. This can be gauged roughly—in the absence of suitable meters—by observing the rate of bubbling through the sulphuric acid which dries the gases before mixing (Gattermann, *Annalen*, 1906, **347**, 372).

This process has been used for the preparation of the alkyl-substituted benzaldehydes, the –CHO group entering the *para* position. Benzene itself does not react easily under these conditions, but does so if aluminium bromide replaces the chloride. It has recently been shown that small amounts of anthracene and its homologues, as well as derivatives of triphenylmethane, may be formed in these reactions (Hey, *J.*, 1935, 72).

4. *Formation of Acids and Amides.*—By the action of phosgene on benzene in presence of aluminium chloride, benzoyl chloride is formed. The method is, however, not a convenient general method for the preparation of acid chlorides, since it is not always easy to prevent the further condensation of the acid chloride to the ketone.

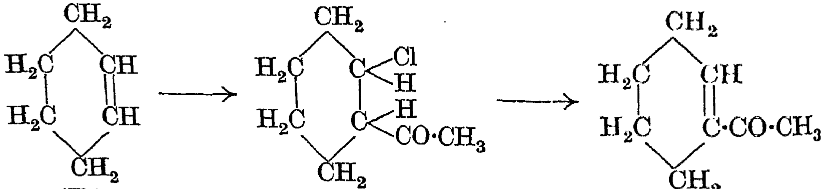
The amides of aromatic acids can be prepared by the condensation of urea chloride, NH_2COCl, with the hydrocarbon under the influence of aluminium chloride. The reagent is prepared as it is required by heating cyanuric acid in a stream of dry hydrogen chloride. The gas is passed directly into the hydrocarbon and aluminium chloride in carbon disulphide (Gattermann, *Ber.*, 1899, **32**, 1117; *Annalen*, 1888, **244**, 29).

Phenyl*iso*cyanate can be made to react with aromatic hydrocarbons in presence of aluminium chloride to give anilides (Leuckart, *Ber.*, 1885, **18**, 873; *J. pr. Chem.*, 1890, [ii], **41**, 301).

The mechanism of the Friedel and Crafts reaction has been the subject of many investigations, yet the function of the aluminium chloride appears to be obscure. While the formation of the alkylbenzenes can be accomplished satisfactorily by the use of only a small amount of aluminium chloride, the ketone synthesis requires at least equimolecular amounts of aluminium chloride and acid chloride if the reaction is to go to completion. The difference may not be the result of different mechanisms, but may be due entirely to the removal of the free aluminium chloride by the ketone as it is formed in the reaction (Perrier, *Ber.*, 1900, **33**, 815; Boeseken, *Rec. trav. chim.*, 1900, **19**, 19; 1901, **20**, 102; Steele, *J.*, 1903, **83**, 1470; Oliver, *Rec. trav. chim.*, 1914, **33**, 91).

An investigation of the mechanism of the reaction from another point of view has been described by Wieland and Bettag (*Ber.*, 1922, **55**, 2246). They show that *cyclo*hexene (X) is able to add on acetyl chloride under the influence of aluminium chloride and that the chloro-ketone (XI) so formed splits off hydrogen chloride with the production of tetrahydroacetophenone (XII). Benzoyl chloride behaves similarly.

It seems not improbable that a similar reaction may occur with benzene, although at present there is no direct evidence in favour of such a conclusion.



(X.) (XI.) (XII.)

(e) *Introduction of other Substituents.*

Alkyl Groups.—Some alcohols react with benzene in presence of sulphuric acid to give homologues of benzene. *iso*Butyl alcohol condenses with benzene and toluene to give *tert.*-butylbenzene and *tert.*-butyltoluene. Benzyl alcohol and *m*-nitrobenzyl alcohol similarly condense under the influence of sulphuric acid to give diphenylmethane and *m*-nitrodiphenylmethane, respectively (V. Meyer and Wurster, *Ber.*, 1873, **6**, 963; Becker, *ibid.*, 1882, **15**, 2091).

Preparation of tert.*-Butylbenzene.*—Fuming sulphuric acid (30%, 1 kg.) is added gradually to a well-cooled mixture of 1 kg. of benzene and 250 g. of *iso*butyl alcohol, which is stirred continuously. After ¾ hour, the acid layer is separated and the hydrocarbon layer is washed with water and distilled. The following yields were obtained from 500 g. of alcohol: 263 g. of *tert.*-butylbenzene; 150 g. of di-*tert.*-butylbenzene (Verley, *Bull. Soc. chim.*, 1898, [iii], **19**, 72).

Amino-Group.—Hydroxylamine hydrochloride condenses with benzene and its homologues under the influence of aluminium chloride to give monoamino-derivatives. The yields are poor and the method is quite unsuited for the preparation of amines (C. Graebe, *Ber.*, 1901, **34**, 1778).

Azo-Group.—Mesitylene couples readily with 2 : 4 : 6-trinitrodiazobenzene sulphate to give 2 : 4 : 6-trinitrobenzeneazomesitylene, $(CH_3)_3C_6H_2N{:}N{\cdot}C_6H_2(NO_2)_3$. Toluene, *m*-xylene, anthracene, and α-methylnaphthalene also appear to react similarly, but with these compounds the products of the reaction have not been isolated (K. H. Meyer and Tochtermann, *Ber.*, 1921, **54**, 2283).

(f) *Stability of Substituents in the Benzene Nucleus.*—In the monosubstituted benzenes, the substituent groups are not easily displaced or eliminated. Thus the monohalogen benzenes, which might be expected, by analogy with the alkyl halides, to undergo replacement by $-NH_2$, $-OH$, $-OAlk$, $-NO_2$, etc., are comparatively inert, and not affected by prolonged boiling with alcoholic or aqueous alkali, or by heating at 100° with ammonia or silver salts. Indeed, the conversion of chlorobenzene into phenol requires the action of an excess of 20% aqueous sodium hydroxide at 300°; at 200° the chlorobenzene is recovered unchanged (K. H. Meyer and Bergius, *Ber.*, 1914, **47**, 3155). Aniline and the phenyl ethers are also very resistant to alkaline hydrolysis. This stability is, however, modified by the presence of other groups, and the effect is most marked with such groups as $-NO_2$, $-CN$, $-CO{\cdot}R$. Of these, the nitro-group has the most pronounced activating effect. The influence of these groups is to make substituents adjacent or *para* more reactive. Thus *o*- and *p*-nitrochlorobenzenes are converted into the corresponding nitrophenols by heating with an excess of aqueous sodium hydroxide, into nitranilines by heating with ammonia under pressure, and into nitroanisoles by treatment with methyl alcoholic solutions of caustic potash. Groups *meta* to the nitro are not made reactive. This is seen from the following table, which gives the percentage of nitrobromobenzenes converted into nitrodialkylaniline by treatment with secondary amines at 183° for 45 minutes.

	ortho.	*meta.*	*para.*	
Diethylamine . .	78·7	0	54·5	(Nagornoff, *J. Russ. Phys. Chem. Soc.*, 1898, **29**, 699).
Dipropylamine . .	88·8	0	21·7	
Diamylamine . .	82	0	13·1	

This loosening effect is intensified by other nitro-groups occupying positions *ortho* or *para* to the halogen, for 2 : 4-dinitrochlorobenzene reacts more readily with aqueous alkali, ammonia, or sodium methoxide than either *o*- or *p*-nitrochlorobenzene. In 2 : 4 : 6-trinitrochloro- or bromo-benzene the halogen is very labile, and can be replaced by –OH merely by treatment with warm dilute alkali. The labile character of the halogen in these compounds enables them to be used conveniently for the preparation of many di- and tri-nitro-compounds, some of which would be otherwise inaccessible. In addition to the replacements already referred to, the halogen may be replaced by –OAr by treatment with metal phenates; $-NH\cdot NH_2$ by the action of hydrazine; –CNS by reaction with thiocyanates, and often by –SH and –S– by treatment with alkali sulphide or hydrosulphide. The labile chlorine in the benzene ring can also react with the sodium derivatives of malonic ester and acetoacetic ester (Borsche, *Annalen*, 1911, **386**, 356; **379**, 152; 1913, **402**, 81).

Preparation of 2 : 4-Dinitrophenylhydrazine.—14 G. of hydrazine sulphate are suspended in 50 c.c. of hot water and 35 g. of potassium acetate added. After boiling for 5 minutes, cool and add 30 c.c. of alcohol to precipitate the inorganic salt. This is collected and washed with 25 c.c. of alcohol. The filtrate and washings are combined and heated with a solution of 20·2 g. of 2 : 4-dinitrochlorobenzene in 100 c.c. of alcohol. After heating under reflux for an hour, the reaction mixture is cooled and the dinitrophenylhydrazine collected (C. F. H. Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2957).

Preparation of 2 : 4-Dinitrophenol.—2 : 4-Dinitrochlorobenzene (10 g.) is heated under reflux with a solution of 13 g. of anhydrous sodium carbonate in 120 c.c. of water for about 24 hours, or until the oil has gone into solution. The dinitrophenol is precipitated by the addition of an excess of dilute acid (compare Clemm, *J. pr. Chem.*, 1870, [ii], **1**, 169).

The reaction of 2 : 4-dinitrochloro- and bromo-benzenes with amines is referred to elsewhere (pp. 271–272). Replacement of the halogen by the alkoxy-group is brought about by the addition of a solution of the requisite amount of potassium hydroxide in the appropriate alcohol to the nitrohalogen benzene dissolved in the same alcohol (compare Willgerodt, *Ber.*, 1879, **12**, 763). The replacement of the halogen by OH or OAc can be achieved using hydrated alkali acetates or alkali salts of other organic acids, in acetamide as a solvent (Kym, *Ber.*, 1899, **32**, 3539; Borsche, *ibid.*, 1917, **50**, 1339).

The nitrated phenyl alkyl ethers in which the nitro-groups are *ortho* and *para* to the alkoxy-group resemble the nitrohalogen benzenes, in that, on warming with aqueous alkali, nitrophenols are produced. The ease with which this occurs increases with the number of nitro-groups, for while *p*-nitroanisole is only slowly converted into *p*-nitrophenol by boiling 10% aqueous caustic soda, 2 : 4 : 6-trinitroanisole is hydrolysed by cold aqueous solutions of the alkali carbonates to give salts of picric acid. The alkoxy-group can also be replaced by the hydrazino-residue by the action of hydrazine, and by substituted amino-groups by reaction with amines (Giua and Cherchi, *Gazzetta*, 1919, **49**, [ii], 152). The *p*-toluenesulphonyl ester of 2 : 4-dinitrophenol behaves similarly (Ullmann and Nádai, *Ber.*, 1908, **41**, 1870). The amino-group of nitranilines can be replaced by hydroxyl by warming with aqueous alkali, or by other amino-groups by heating with amines, if there are nitro-groups situated *ortho* or *para* to it.

The activating influence of nitro-groups is also found in polynitro-compounds, and here the nitro-group which suffers replacement is that which has other nitro-groups situated *ortho* and *para* to it. The following examples illustrate the general type of the reaction. Dinitrobenzene is converted into *o*-nitrophenol by heating with aqueous alkali, and is converted slowly into *o*-nitraniline by the action of alcoholic ammonia at room temperature; at 100° the reaction is complete in 2 hours (Laubenheimer, *Ber.*, 1876, **9**, 1826; 1878, **11**, 1155). 2 : 3-Dinitrotoluene reacts similarly with alcoholic ammonia to give *m*-nitro-*o*-toluidine; 2 : 5-dinitrotoluene gives 5-nitro-*o*-toluidine as the principal product (Kenner and Parkin, *J.*, 1920, **117**, 852). 1 : 2 : 3-Trinitrobenzene reacts with sodium methoxide rapidly to give 2 : 6-dinitroanisole; 1 : 2 : 4-trinitrobenzene similarly yields 2 : 4-dinitroanisole (Hollemann and van Haeften, *Rec. trav. chim.*, 1921, **40**, 67). For the reactions of trinitro-compounds with hydrazine see Giua (*Gazzetta*, 1919, **49**, [ii], 166).

The action of the nitro-group is not confined to loosening amino-, nitro-, halogen, or alkoxy-groups, for it is able to make methyl groups *ortho* or *para* to it capable of condensing with aldehydes, esters, and some nitroso-compounds under suitable conditions.

o- and *p*-Nitrotoluene condense with oxalic ester in presence of potassium ethoxide to give nitrophenylpyruvic ester (Reissert, *Ber.*, 1897, **30**, 1030; Reissert and Scherk, *ibid.*, 1898, **31**, 387; W. Wislicenus and Thoma, *Annalen*, 1924, **436**, 45).

$$NO_2{\cdot}C_6H_4{\cdot}CH_3 + EtO_2C{\cdot}CO_2Et \rightarrow NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CO{\cdot}CO_2Et + EtOH$$

Under the influence of secondary amines 2 : 4-dinitrotoluene condenses with benzaldehyde to give 2 : 4-dinitrostilbene according to the following scheme (Thiele and Escale, *Ber.*, 1901, **34**, 2842; Borsche, *Annalen*, 1911, **386**, 351).

$$(NO_2)_2C_6H_3{\cdot}CH_3 + Ph{\cdot}CHO \longrightarrow (NO_2)_2C_6H_4{\cdot}CH{:}CH{\cdot}Ph + H_2O$$

p-Nitrosodimethylaniline condenses with 2 : 4-dinitrotoluene to give dinitrobenzylidene-*p*-aminodimethylaniline. The reaction goes smoothly, and as the product is hydrolysed easily by acid to give 2 : 4-dinitrobenzaldehyde, it is a very convenient method for the preparation of this substance (Sachs and R. Kempf, *Ber.*, 1902, **35**, 1224; Bennett and W. L. C. Pratt, *J.*, 1929, 1466).

$$(NO_2)_2C_6H_4\cdot CH_3 + NO\cdot C_6H_4NMe_2 \longrightarrow (NO_2)_2C_6H_4\cdot CH{:}N\cdot C_6H_4NMe_2 + H_2O$$

Preparation of 2 : 4-Dinitrobenzaldehyde from 2 : 4-Dinitrotoluene.—88 G. of *p*-nitrosodimethylaniline and 91 g. of 2 : 4-dinitrotoluene dissolved in about 500 c.c. of 96% alcohol are heated on a boiling water-bath after the addition of 10 g. of sodium carbonate. The colour gradually changes from dark green to red-brown, and the condensation product separates, so that the mixture becomes almost solid. After cooling, the product is drained at the pump and washed with several litres of boiling water. The yield of crude material is about 130 g., and it may be used directly for hydrolysis without any purification.

To this end, the crude condensation product (100 g.) is covered with a solution of 125 g. of concentrated hydrochloric acid in 125 g. of water and the mixture boiled, steam being passed in to ensure vigorous agitation. After keeping at the boiling point for 3—5 minutes, the whole mass is cooled, the aqueous liquor removed, and the solid remelted as before under a fresh portion of the same acid. The solid product is finally washed with water and dried. It is purified by crystallisation from light petroleum (b. p. 90—110°), m. p. 72°

The behaviour of 2 : 4-dinitrophenol and 2 : 4 : 6-trinitrophenol with phosphorus pentachloride to give comparatively good yields of the corresponding chloro-compounds is another example of the effect of nitro-groups on the reactivity of substituents (Engelhardt and Latschinoff, *Ber.*, 1870, **3**, 98; Clemm, *J. pr. Chem.*, 1870, [ii], **1**, 154). This reaction only proceeds with difficulty in the case of phenol. That the hydroxyl of the nitrophenols can be replaced more readily than that of phenol itself is further shown by the formation of picryl chloride by the action of toluenesulphonyl chloride and diethylaniline on picric acid. 2 : 4-Dinitrophenol reacts similarly, but the yield of dinitrochlorobenzene is not so good. The toluenesulphonyl esters of *o*-nitrophenol and 2 : 4-dinitrophenol can react with aniline and other primary amines to give nitroamines (Ullmann and Nádai, *Ber.*, 1908, **41**, 1870).

Preparation of Picryl Chloride from Picric Acid.—Picric acid (11·5 g.) is heated for 8 hours on a water-bath with 9·5 g. of toluenesulphonyl chloride, 8 g. of freshly distilled diethylaniline, and 9 g. of nitrobenzene. The product is acidified, and steam distilled to remove nitrobenzene. The residue, insoluble in water, is crystallised from alcohol and then consists of pure picryl chloride, m. p. 83°.

An interesting type of reaction which further illustrates the activating influence of nitro-groups is the behaviour of dinitro-compounds with hydroxylamine, in presence of alcoholic ethylate. *o*- and *p*-Dinitrobenzene yield quinonoid salts probably of the type $NO_2K{:}C_6H_4{:}NO_2K$, while with *m*-dinitrobenzene an amino-group is introduced into the nucleus giving 2 : 4-dinitroaniline and 2 : 4-

dinitro-*m*-phenylenediamine (Meisenheimer and Patzig, *Ber.*, 1906, **39**, 2533).

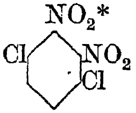
Preparation of 2 : 4-*Dinitro*-m-*phenylenediamine*.—A filtered solution of hydroxylamine, prepared by the addition of an excess of an alcoholic solution of sodium ethoxide to 1 g. of hydroxylamine hydrochloride, is added to 1 g. of *m*-dinitrobenzene. The precipitate which separates is just dissolved by the addition of water and the solution cooled strongly. 2 : 4-Dinitro-1 : 3-diaminobenzene separates out, yield 90% of theory. The mother-liquor contains a little 2 : 4-dinitraniline.

The nitro-groups have evidently rendered the *ortho* and *para* hydrogens more easily substituted. A somewhat similar phenomenon is observed in the behaviour of *m*-dinitro-compounds with potassium cyanide. *m*-Dinitrobenzene, heated in alcoholic solution with potassium cyanide, is converted first into 2 : 6-dinitrobenzonitrile and by the further action of the cyanide into 2-nitro-6-methoxybenzonitrile. 2 : 4-Dinitrochlorobenzene under similar conditions yields successively 2 : 4-dinitro-3-cyanochlorobenzene and 2-nitro-3-cyano-4-methoxychlorobenzene.

It has been found that groupings $-CO_2H$, $-CHO$, $-SO_3H$, $-CN$, $-CO{\cdot}R$ are able to confer mobility on a halogen atom situated *ortho* or *para* to them, but the effect appears to be less marked than with the nitro-group (Schöpff and co-workers, *Ber.*, 1889, **22**, 900, 3281; 1890, **23**, 3440, 3445, 3451; 1891, **24**, 3771, 3785, 3808; Borsche, Stackmann, and Makaroff-Semljanski, *ibid.*, 1916, **49**, 2222).

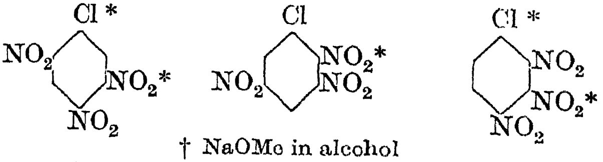
It will be observed that the groups which have an activating influence on substituents *ortho* and *para* to them are those which are *meta*-directing. It might therefore seem not improbable that groups which are *ortho*- and *para*-directing should exert an activating influence on substituents situated in the *meta* position. There is evidence in support of this supposition, although the effect is less pronounced than that due to the nitro-group (Kenner, *J.*, 1914, 2717; Kenner and Parkin, *ibid.*, 1920, 852; Burton and Kenner, *ibid.*, 1922, 489), and the volume of experimental work is comparatively slender. The contrast in the activating action of $-Cl$ and $-NO_2$ groups is seen by comparing the behaviour of the three trichlorobenzenes and the trinitrobenzenes with sodium methoxide. While 1 : 3 : 5-trichlorobenzene reacts more readily than either of its isomers to give 3 : 5-dichloroanisole, 1 : 3 : 5-trinitrobenzene is the least reactive of the trinitrobenzenes towards sodium methoxide (Hollemann, *Rec. trav. chim.*, 1918, **37**, 195; Hollemann and van Haeften, *ibid.*, 1921, **40**, 67). Another example which suggests that the chloro-group activates in the *meta* position is the formation of 2-chloroanisaldehyde from 4-nitro-2-chlorobenzaldehyde by reaction with sodium methoxide in methyl alcohol (Tiemann, *Ber.*, 1891, **24**, 709). Some further examples have been given by Burton and Kenner (*J.*, 1922, 489).

Many of the apparently irregular replacements in aromatic compounds containing methyl, halogen, and nitro-groups may in part be due to the loosening effect of halogen and methyl. These may either enhance or partially neutralise that of the nitro-groups. After taking these factors into consideration, the replacement may often take an unexpected course. The following examples, taken from the literature, indicate the difficulty of predicting with certainty which group is replaceable.



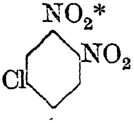
† alc. NH_3

Hollemann, *Rec. trav. chim.*, 1920, **39**, 736.



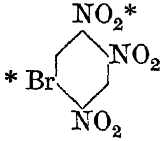
† NaOMe in alcohol

van de Vliet, *Rec. trav. chim.*, 1924, **43**, 606.



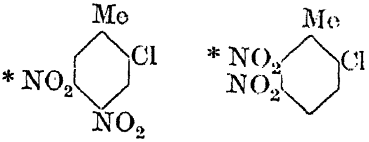
† alc. NH_3

Laubenheimer, *Ber.*, 1876, **9**, 1826.



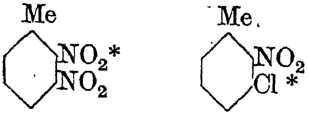
† NaOMe in alcohol

Giua, *Gazzetta*, 1921, **51**, i, 307.



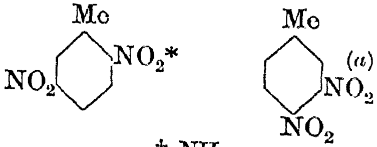
† Amines or NH_3

Morgan and Drew, *J.*, 1920, **117**, 788; Morgan and L. A. Jones, *J.*, 1921, **119**, 191.



† NH_3

Burton and Kenner, *J.*, 1921, **119**, 1047.



† NH_3

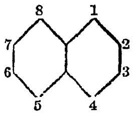
Kenner and Parkin, *J.*, 1920, **117**, 852.

* Group principally replaced.
† Reagent employed.
(*a*) Product contains 61% 3-nitro-*p*-toluidine and 39% 4-nitro-*m*-toluidine.

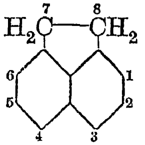
It has been suggested (Kenner, *J.*, 1914, 2717) that the replacement requires the intermediate formation of an additive compound, and that the point of attachment is determined not only by considerations of unsaturation, but also by the steric configuration of the molecule (Burton and Kenner, *loc. cit.*).

(2) *Polycyclic Aromatic Hydrocarbons.*

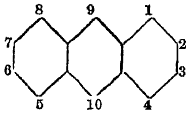
The hydrocarbons considered in this section are those composed of two or more benzene rings fused together so that each pair of rings has two carbon atoms in common. The more common types of polycyclic hydrocarbons are formulated below, together with the system of numbering adopted.



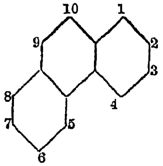
Naphthalene.



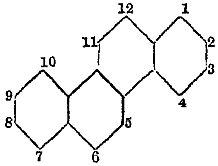
Acenaphthene.



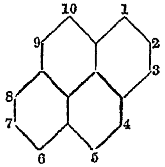
Anthracene.



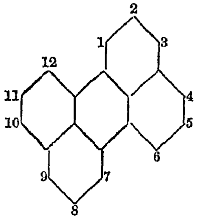
Phenanthrene.



Chrysene.



Pyrene.



Perylene.

These hydrocarbons display additive properties in varying degrees. They can be reduced more or less readily. They form addition compounds with some polynitro-compounds. They also add on halogens under suitable conditions, and some are also able to combine additively with nitric and nitrous acids.

In spite of this tendency they undergo substitution quite readily and most of their derivatives are obtained by this means.

1. *Additive Reactions.*

The addition of hydrogen can be accomplished by treatment with sodium and an alcohol, but under these conditions the reduction appears to be restricted to the addition of two or four atoms of hydrogen. Thus naphthalene in ethyl alcohol is reduced by sodium to the 1 : 4-dihydride; in amyl alcohol the 1 : 2 : 3 : 4-tetrahydride is formed. Anthracene and phenanthrene in amyl alcohol yield dihydrides.

Preparation of 1 : 4-*Dihydronaphthalene.*—A boiling solution of 15 g. of naphthalene in 300 c.c. of commercial absolute alcohol is run slowly on to 22·5 g. of sliced sodium in a round-bottomed 2-l. flask and the solution boiled till the metal dissolves. The greater part of the alcohol is recovered by distillation through a fractionating column, and the dihydronaphthalene is driven over by a current of steam, and taken up from the distillate by ether. Dihydronaphthalene is obtained as an oil, b. p. 210°, which solidifies on cooling. It usually contains a small proportion of naphthalene (Bamberger and Lodter, *Annalen*, 1895, **288**, 75).

The reduction of naphthalene can also be effected catalytically, to give under suitable conditions either 1 : 2 : 3 : 4-tetrahydronaphthalene or the fully hydrogenated product decahydronaphthalene (Leroux, *Compt. rend.*, 1904, **139**, 672; Willstätter and Seitz, *Ber.*, 1923, **56**, 1388; *ibid.*, 1924, **57**, 683; Zelinski, *ibid.*, 1923, **56**, 1723).

Anthracene and phenanthrene can be reduced by treatment with sodium and amyl alcohol to give dihydro-derivatives (Graebe and Liebermann, *Annalen*, Spl., 1870, **7**, 266; J. Schmidt and Mezger, *Ber.*, 1906, **40**, 4247). The reduction can be carried further either by heating with phosphorus and hydriodic acid, or catalytically (Godchot, *Compt. rend.*, 1904, **139**, 604; Schroeter, van Hulle, and H. Müller, *Ber.*, 1923, **57**, 2025).

The formation of bromo and chloro addition compounds of naphthalene, anthracene, and phenanthrene has been recorded, but these compounds tend to eliminate the elements of halogen hydride, either on warming or on treatment with alkali, giving the corresponding halogen-substituted hydrocarbons (compare W. H. Perkin, *Chem. News*, 1876, **34**, 145; Austin, *J.*, 1908, **93**, 1763).

The addition of nitric acid and oxides of nitrogen to anthracene is considered in the section dealing with the nitration of anthracene (p. 63).

Nitro-compounds such as picric acid, styphnic acid, and 1 : 3 : 5-trinitrobenzene combine with the polycyclic aromatic hydrocarbons to give crystalline additive compounds, which can be purified by crystallisation from suitable solvents. They serve for the characterisation of these hydrocarbons, and can also be used to isolate them from mixtures. The formation of picrates has also been recommended for the estimation of naphthalene and acenaphthene (F. W. Küster, *Ber.*, 1894, **27**, 1101). Phenanthrene may also be estimated as picrate by the method of Anschütz and G. Schultz (*Annalen*, 1879, **196**, 43) as modified by Lunge ("Coal Tar and Ammonia," 1916, p. 643). It should be noted, however, that the picrates of these hydrocarbons display unequal stabilities in different solvents. The picrates of acenaphthene and naphthalene, which can be prepared by warming the hydrocarbon with an aqueous solution of picric acid, may be crystallised unchanged from alcohol; anthracene picrate crystallises well from benzene, but is decomposed by alcohol.

2. *Oxidation.*

In comparison with benzene, the polycyclic hydrocarbons are oxidised comparatively easily. Chromic acid in glacial acetic acid converts them more or less readily into quinones. Anthracene yields anthraquinone quantitatively, and this reaction is employed for the quantitative estimation of anthracene. Chrysene also may be converted into the quinone almost quantitatively under suitable conditions. Acenaphthene, on the other hand, yields a quinone which is oxidised very readily to naphthalic acid, so that the yield of acenaphthaquinone is usually small. The formation of phenanthraquinone by the oxidation of phenanthrene with chromic oxide is also accompanied by the oxidation product of the quinone, diphenic acid, but the formation of the quinone proceeds more smoothly by using iodic acid as the oxidising agent.

Preparation of Anthraquinone.—Anthracene (10 g.) is dissolved in 120 c.c. of boiling glacial acetic acid, and a solution of 20 g. of chromic oxide in 15 c.c. of water and 75 c.c. of glacial acetic acid is added drop by drop over a period of about 1 hour. The mixture is cooled and the oxidised product obtained by pouring the solution into about ½ l. of water. The precipitated anthraquinone is collected, washed with hot water, then with dilute alkali, and again with water. The yield of dried anthraquinone is about 10 g. If pure anthracene was used for the oxidation, the quinone is best purified by sublimation. When the starting point is crude anthracene, pure anthraquinone can be obtained by heating the dried crude quinone with about 5 times its weight of 10% fuming sulphuric acid for 10 minutes at 100°, and then leaving the mixture for 12 hours in a moist place. The pure anthraquinone is precipitated by pouring into water. The precipitate is collected, washed with hot dilute caustic soda solution, then with water, and dried in a steam oven.

Preparation of Phenanthraquinone.—A solution of 2·2 parts of chromic oxide in 5—6 parts of warm glacial acetic acid is added gradually to phenanthrene dissolved in 4—5 parts of glacial acetic acid. The oxidation is completed by warming under reflux for a short time. The greater part of the solvent is recovered by distillation and the residue poured into water. The precipitate thus obtained is collected, washed with alkali and water, and then stirred with an excess of sodium bisulphite solution to extract the quinone. Phenanthraquinone is precipitated from the bisulphite solution by the addition of dilute acid, and purified by crystallisation from alcohol, benzene, or acetic acid, m. p. 205° (Graebe, *Annalen*, 1873, **167**, 139).

The oxidation of phenanthrene to the quinone can also be accomplished by heating with iodic acid in acetic acid solution. This method has been used for the quantitative determination of the hydrocarbon in commercial specimens (Williams, *J. Amer. Chem. Soc.*, 1921, **43**, 1918).

Preparation of Chrysenequinone.—A thin paste of 50 g. of finely-powdered chrysene in 1 kg. of glacial acetic acid is heated to boiling and a solution of 100 g. of chromic oxide in 1 kg. of glacial acetic acid is added gradually over a period of 8—10 hours. It is advisable that no chromic acid should be added till that previously introduced has been completely reduced. After all the oxidising agent has been added, a considerable part of the chrysenequinone separates out as orange-red prisms on cooling. The remainder is obtained by distilling off the greater part of the solvent, and diluting the residue with water. The yield of quinone by this method is stated to be 96—97% (Bamberger and Burgdorf, *Ber.*, 1890, **23**, 2433).

3. *Substitution.*

It is intended to summarise here the behaviour of some of the better known polycyclic hydrocarbons towards substitution. With the exception of naphthalene, the information available on the reactions of the polycyclic hydrocarbons is comparatively scanty, and in many respects unsatisfactory.

(a) *Naphthalene.* The introduction of halogen or nitro-group by the usual processes occurs at the α-position without the formation of any serious amounts of the isomeric β-compound. A second substituent also enters one of the free α′-positions. The nitration of α-nitronaphthalene gives a mixture of 1 : 5- and 1 : 8-dinitronaphthalene; while 1 : 4- and 1 : 5-dihalogen naphthalenes result by the further halogenation of the α-chloro- and bromo-naphthalenes.

The behaviour of naphthalene towards sulphonation is interesting. By reaction with cold fuming sulphuric acid or with concentrated sulphuric acid at about 50—80°, naphthalene-α-sulphonic acid is formed. Sulphonation with concentrated sulphuric acid at higher temperatures gives increasing amounts of the β-acid. This is shown by the following table, due to Euwes (*Rec. trav. chim.*, 1909, 28, 298).

Temperature.	80°.	100°.	129°.	150°.
Naphthalene recovered after 8 hours, %	27	20	10	6·4
Product contains % of *α* acid . .	96·4	83·2	44·4	18·3
,, ,, ,, *β* ,, . .	3·6	16·8	55·6	81·7

Apparently, the α-sulphonic acid is produced first, or at least more easily, and undergoes conversion into the β-acid by the action of the hot concentrated sulphuric acid (compare the behaviour of benzene *m*-disulphonic acid, p. 41).

Preparation of Naphthalene-β-sulphonic Acid.—400 G. of concentrated sulphuric acid are added to 250 g. of naphthalene maintained at 160° and the temperature is kept constant for 20 minutes. The mixture is then allowed to cool for a short time and poured into 300 c.c. of water. On cooling, nearly all the *β*-acid separates out as trihydrate. It can be purified by dissolving in half its weight of water at 70° and adding approximately $\frac{1}{6}$ of its weight of concentrated hydrochloric acid. The pure *β*-acid separates out on cooling (Witt, *Ber.*, 1915, 48, 743).

The introduction of a second sulphonic group occurs in a position as remote as possible from the first one. Here also the experimental conditions determine the configuration of the final product. At lower temperatures, the α-sulphonic acid gives 1 : 5-disulphonic acid, while the β-acid yields the 2 : 5-disulphonic acid. At higher temperatures, a mixture of 2 : 7-, 2 : 6-, and 2 : 5-acids results.

The formation of alkylnaphthalenes by the application of the Friedel–Crafts reaction does not proceed smoothly. The ethyl halides and their immediate homologues yield a mixture of the corresponding alkyl naphthalenes, the β-compound predominating. The product always contains ββ′-dinaphthyl and other substances produced by the action of aluminium chloride on naphthalene. For the preparation of ketones from naphthalene by the Friedel–Crafts reaction see Samuelson (*Svensk. Kem. Tidskr.*, 1922, 34, 7).

The substitution products of naphthalene bear a general resemblance in their reactions to the corresponding derivatives of benzene. The halogen naphthalenes are not seriously acted on by warm aqueous alkali. The hydroxy-derivatives are feeble acids dissolving in aqueous alkali to give salts and coupling with diazonium salts. The amines can be diazotised.

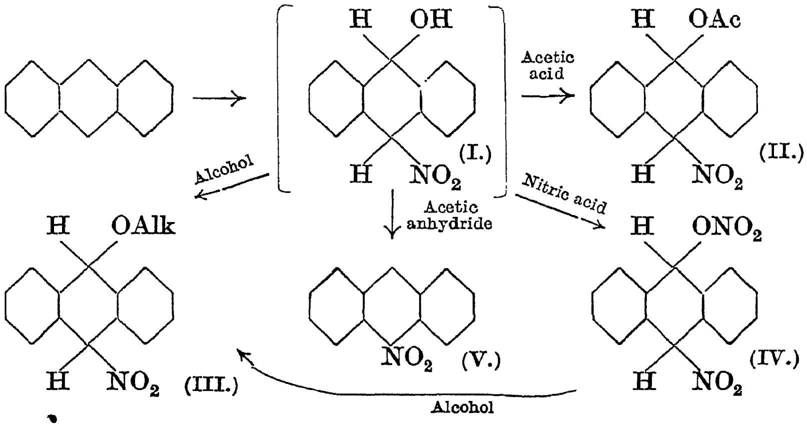
There are, however, some important differences between the respective behaviour of naphthalene and benzene, one of the most striking being the ready interconversion of the hydroxy- and amino-compounds. Aminonaphthalenes, by heating with aqueous sodium bisulphite, or with aqueous sodium hydroxide or aqueous acids, are converted into the corresponding hydroxynaphthalenes, which may be reconverted into aminonaphthalenes by warming with ammonium sulphite solution. These reactions are dealt with more fully on pp. 86 and 287.

For a complete account of the chemistry of naphthalene and its derivatives, the article on " Naphthalene " in Thorpe's " Dictionary of Applied Chemistry " should be consulted.

(b) *Anthracene.* The behaviour of anthracene towards substitution is very interesting. The reactive positions are those situated between the two benzene nuclei, and there is strong evidence that substitution in these positions by $-NO_2$ and halogens is preceded by addition. The formation of anthracene 9 : 10-dichloride and dibromide by direct combination with the halogen and the subsequent elimination of the elements of halogen hydride to give 9-chloro- or bromo-anthracene have already been referred to (see p. 60). The substitution of halogen in other positions requires more drastic conditions (K. H. Meyer and Zahn, *Annalen,* 1913, **396**, 166).

The nitration of anthracene has long been known to be abnormal, for the type of product obtained appeared to depend in no very obvious manner on the experimental conditions (A. G. Perkin, *J.*, 1891, 59, 634; Perkin and J. E. McKenzie, *ibid.*, 1892, **61**, 865; Dimroth, *Ber.*, 1901, **34**, 221). The structure of its nitration products of anthracene have been reviewed by Meisenheimer and Connerade (*Annalen,* 1904, **330**, 133) and it is now possible to present a rational account of its behaviour with nitric acid.

Apparently the first product of the action of nitric acid is the formation of dihydronitroanthranol (I), which is converted into the acetate (II) provided that the anthracene is acted on by an acetic acid solution of nitric acid. In alcohol, the ether (III) is formed, while an excess of nitric acid yields the nitrate (IV). Nitration in acetic anhydride solution yields 9-nitroanthracene (V), presumably by the dehydration of dihydronitroanthranol.



Although halogens and nitric acid attack the 9 and 10 positions, sulphonation gives anthracene α- and β-sulphonic acids. The recorded observations on the sulphonation of anthracene are, however, often confusing and contradictory, but it appears that sulphonation at comparatively low temperatures favours the formation of the α-acid, while at higher temperatures more of the β-acid is produced (Heffter, *Ber.*, 1895, **28**, 2258; Bayer and Co., D.R.-P. 251,695; Liebermann, *Annalen*, 1882, **212**, 43; *Ber.*, 1879, **12**, 182).

The application of the Friedel–Crafts reaction to anthracene is apparently limited to the introduction of the benzoyl group, but even the information on this point is incomplete (Perrier, *Ber.*, 1900, **33**, 816; Lippmann and Fleissner, *ibid.*, 1899, **32**, 2249; Lippmann and Keppich, *ibid.*, 1900, **33**, 3086).

(c) *Acenaphthene.* Substituting reagents appear to attack the nucleus of acenaphthene almost exclusively. Thus bromination, chlorination, iodination, nitration or sulphonation under the usual conditions furnish mono-derivatives of acenaphthene with the substituent group in position 3. It seems, however, that by nitrating with benzoyl nitrate, or by sulphonating with chlorosulphonic acid, the substituent enters position 1. An interesting observation has been made by Morgan and Sheasby (*J.S.C.I.*, 1925, **44**, 408T.). They point out that 1-nitroacenaphthene is converted into the isomeric 3-nitro-compound by warming in glacial acetic acid with the addition of mineral acid.

The Friedel–Crafts reaction can be applied to acenaphthene for the formation of alkyl derivatives (F. Mayer and Kaufmann, *Ber.*, 1920, **53**, 289) and ketones (Graebe, *Annalen*, 1903, **327**, 91; Fleischer and Wolff, *Ber.*, 1920, **53**, 925; Mayer and Kaufmann, *loc. cit.*).

(d) *Phenanthrene.* Substitution in phenanthrene occurs preferentially in positions 9 and 10. Thus bromination or chlorination yields first 10-bromo- or chloro-phenanthrene, presumably through the intermediate formation of the 9 : 10-dihalogen addition compound (Sandquist and Hagelin, *Ber.*, 1918, **51**, 1515; Austin, *J.*, 1908, **93**, 1763). The action of 2 or 3 mols. of bromine on phenanthrene has been studied exhaustively by Henstock (*J.*, 1921, **119**, 55; 1923, **123**, 3097), who isolated a number of dibromo-derivatives such as 2 : 10-, 4 : 10-, 6 : 10-, 8 : 10-, and 2 : 7-dibromophenanthrene.

Using nitric acid in glacial acetic acid, 10-nitrophenanthrene is formed as the principal product, together with some 4-nitro- and 2-nitro-phenanthrenes (J. Schmidt and Heinle, *Ber.*, 1913, **44**, 1488). As with naphthalene, the result of the sulphonation of phenanthrene is determined by the experimental conditions. At about 95—100°, phenanthrene-10-sulphonic acid is formed, at 120—130° a mixture of the 2- and 3-sulphonic acids is formed (A. Werner, *Annalen*, 1902, **321**, 248; Sandquist, *ibid.*, 1911, **379**, 79).

A very full account of phenanthrene, acenaphthene, and related hydrocarbons and their derivatives can be found in "The Higher Coal-Tar Hydrocarbons," by A. E. Everest. For further information on the chemistry of anthracene "Anthracene and Anthraquinone," by Barnett, should be consulted.

TABLE I.

Physical Constants of the Paraffins and cyclo*Hexanes.*

		B. p.	*d.*	n_D.
Tetramethylmethane	C_5H_{12}	9·5°	—	—
β-Methylbutane	—	31	$0{\cdot}639^{0}$	—
n-Pentane	—	36	$0{\cdot}634^{15}$	—
ββ-Dimethylbutane	C_6H_{14}	49	$0{\cdot}666^{0}_{0}$	—
Di*iso*propyl	—	58	$0{\cdot}679^{0}_{4}$	—
β-Methylpentane	—	61	$0{\cdot}677^{0}_{0}$	—
γ-Methylpentane	—	64	$0{\cdot}668^{19}_{4}$	$1{\cdot}381^{19}$
n-Hexane	—	69	$0{\cdot}677^{0}_{4}$	$1{\cdot}375^{20}$
*cyclo*Hexane	C_6H_{12}	81	$0{\cdot}779^{19{\cdot}5}_{4}$	—
β-Methylhexane	C_7H_{16}	89	$0{\cdot}707^{0}_{4}$	—
n-Heptane	—	98	$0{\cdot}708^{0}_{0}$	$1{\cdot}3867^{17{\cdot}6}$
Methyl*cyclo*hexane	C_7H_{14}	102	$0{\cdot}766^{18{\cdot}5}_{4}$	—
Di*iso*butyl	C_8H_{18}	108	$0{\cdot}710^{0}_{4}$	$1{\cdot}3935^{25}$
*iso*Octane	—	116	$0{\cdot}704^{15}_{15}$	$1{\cdot}3944^{25}$
1 : 3-Dimethyl*cyclo*hexane	C_8H_{16}	120	$0{\cdot}774^{15}_{0}$	—
1 : 4-Dimethyl*cyclo*hexane	—	120	$0{\cdot}769^{20}_{4}$	—
1 : 2-Dimethyl*cyclo*hexane	—	124	$0{\cdot}800^{0}_{0}$	—
n-Octane	C_8H_{18}	126	$0{\cdot}718^{0}_{4}$	$1{\cdot}4029^{20{\cdot}6}$
1 : 3 : 5-Trimethyl*cyclo*hexane	C_9H_{18}	138	$0{\cdot}759^{20}_{4}$	—
n-Nonane	C_9H_{20}	150	$0{\cdot}733^{0}_{4}$	—
Di*iso*amyl	$C_{10}H_{22}$	159	—	—
Menthane	$C_{10}H_{20}$	170	—	—
n-Decane	$C_{10}H_{22}$	173	—	—

	B. p.	d.	
Butadiene	$-5°$	—	Br in $CHCl_3$ → 2-tetrabromides, m. p. 118° and 39°.
*iso*Propylethylene . .	21	0·648	Dibromide, b. p. 74—75°/20 mm.
2-Methyl-Δ^{2}-butene . .	31	0·667$^{0}_{0}$	Dibromide, b. p. 172—174°.
Isoprene	34	0·699$^{15}_{15}$	Tetrabromide, oil.
Δ^{2}-Pentene . . .	36	—	Dibromide, b. p. 178°.
Trimethylethylene . .	38	0·727	Dibromide, b. p. 64°/17 mm.; NOCl, m. p. 74—75°.
*cyclo*Pentadiene . . .	41	0·806$^{16}_{4}$	1 mol. Br in $CHCl_3$ → *cis*- and *trans*-dibromides; *cis*, liquid; *trans*, m. p. 45°; tetrabromide, liquid. Hydrocarbon readily polymerises → di*cyclo*pentadiene.
$\Delta^{1:3}$-Pentadiene . . .	43	0·691$^{16}_{4}$	Br → 2-tetrabromides, m. p. 115°; liq.
Diallyl	59	0·698$^{12}_{4}$	Br → 2-tetrabromides, m. p. 64°; 53°.
2 : 3-Dimethylbutadiene .	70	0·730$^{16}_{4}$	Dibromide, m. p. 137°.
Tetramethylethylene . .	73	0·712	Dibromide, m. p. 121°; NOCl,* m.p. 121°, blue.
*cyclo*Hexadiene . . .	80	0·840$^{20}_{4}$	
*cyclo*Hexene . . .	83	0·810$^{20}_{4}$	NOCl, m. p. 152—153°.
Methyl-Δ^{3}-*cyclo*hexene . .	102	0·800$^{20}_{0}$	NOCl, liquid.
Methyl-Δ^{1}-*cyclo*hexene . .	111	0·802$^{20}_{0}$	NOCl, m. p. 98°; nitrosate, m. p. 115°.
Phenylacetylene . . .	140	0·930$^{20}_{4}$	Na deriv. by action of Na on ether sol. Ag and Cu derivs. by action of alc. soln. of hydrocarbon on ammoniacal Ag or Cu salts.
Styrene	144	0·907$^{20}_{4}$	Polymerises to glass-like mass; NOCl, m. p. 97°; nitrosite (prep. in ether soln.), m. p. 129°.
Bornylene	146	—	M. p. 110°, $[\alpha]_D$ $-22°$ (c, 10, toluene).
α-Thujene	152	—	
α-Pinene	155	0·856$^{20}_{4}$	HCl in glacial HAc → dipentene dihydrochloride. NOCl, m. p. 115°.
Fenchene	156	0·869	Dibromide, m. p. 87—88°.
Camphene	160	—	M. p. 48—52°.
Sabinene	162—166	—	HCl in glacial HAc → terpinene dihydrochloride.
Δ^{3}-*p*-Menthene . . .	167	—	
β-Phellandrene . . .	171 † 57/11 mm.	—	α-Nitrosite, m. p. 102°; β-nitrosite, m. p. 97°.‡
α-Phellandrene . . .	175 † 59/11 mm.	—	α-Nitrosite, m. p. 121°; β-nitrosite, m. p. 105°.§
Sylvestrene	175	0·848^{18}	$[\alpha]_D$ + 68°. Tetrabromide, m. p. 135—136°; NOCl, m. p. 106—107°; dihydrochloride, m. p. 73°.
Carvestrene	175	—	Dihydrochloride, m. p. 73°.
Dipentene	176	0·841$^{21}_{4}$	Inactive; tetrabromide, m. p. 104°; NOCl, m. p. 78°; nitrosate, m. p. 84°; nitrolpiperidine, m. p. 154°; dihydrochloride, m. p. 50°.
Limonene	176	0·841$^{21}_{4}$	$[\alpha]_D$ + 126°. Tetrabromide, m. p. 104°; α-NOCl, m. p. 103°; α-nitrolpiperidine, m. p. 93°; β-NOCl,‖ m. p. 105°; β-nitrolpiperidine, m. p. 110°; dihydrochloride, m. p. 50°.
α-Terpinene	180	0·834$^{20}_{4}$	Dihydrochloride, m. p. 51°; nitrosite, m. p. 155°.
γ-Terpinene	183	0·835$^{15}_{4}$	Tetrabromide, m. p. 128°; NOCl, m. p. 111°.
Indene	181	1·006$^{4}_{4}$	Polymerises. Br in ether at 0° → dibromide, m. p. 32°; α-nitrosite, m. p. 107—109°; β-nitrosite, m. p. 136°; picrate, explosive.
Terpinolene	184	0·854	Tetrabromide, m. p. 116°.
1 : 2-Dihydronaphthalene .	212	—	M. p. 25°. Dibromide, m. p. 74°.
Di*cyclo*pentadiene . . .	88/35 mm.	—	NOCl, m. p. 182°. Hydrocarbon → *cyclo*pentadiene on distillation at 760 mm.
1-Phenyl-$\Delta^{1:3}$-butadiene . .	90/15 mm.	0·933$^{15}_{4}$	Polymerises on distillation at 760 mm.; Br → 2-tetrabromides, m. p. 151° and 76°.
Stilbene	360	—	M. p. 122°.

TABLE III.

The Physical Constants of the Benzenoid Hydrocarbons and some of their Derivatives.

			M. p. of principal nitration products.		Sulphonyl derivatives. M. p.	
	B. p.	M. p.	Di-.	Tri-.	Chloride.	Amide.
Benzene	80°	5°	90°	122°	14°	148°
Toluene	110	—	70	82	69 (*f*)	137
Ethylbenzene	136	—	oil	37	—	—
p-Xylene	138	13	123 (*a*) 93 (*b*)	139	25	147
m-Xylene	139	—	92 (*c*) 82 (*d*)	182	34 (*f*)	137
o-Xylene	142	—	29 (*e*)	—	51 (*f*)	144
*iso*Propylbenzene	152	—	—	109	—	107(*f*)
n-Propylbenzene	158	—	—	—	—	110(*f*)
p-Ethyltoluene	162	—	—	92	—	—
Mesitylene	163	—	86	231	57	141
tert.-Butylbenzene	166	—	—	108	—	137(*f*)
ψ-Cumene	168	—	—	185	61	181(*g*)
*iso*Butylbenzene	170	—	—	—	—	—
sec.-Butylbenzene	173	—	—	—	—	—
p-Cymene	175	—	—	118	—	
Hemellithene	175	—	—	—	—	—
Hydrindene	177	—	—	—	—	—
n-Butylbenzene	180	—	—	—	—	—
m-*tert.*-Butyltoluene	187	—	—	97*	—	94
Durene	193	80	—	—	99	155
*iso*Durene	196	—	156	—	—	142
5-*tert.*-Butyl-*m*-xylene	201	—	68	110*	—	141
Prehnitene	204	—	176	—	—	177 187 (*h*)
Pentamethylbenzene	231	52	—	—	82	186
Diphenyl	254	70	—	—	—	—
Diphenylmethane	261	27	—	—	—	—
Hexamethylbenzene	264	164	—	—	—	—
αβ-Diphenylethane	284	52	—	—	—	—
Triphenylmethane	358	92	—	—	—	—

(*a*) 2 : 3-Dinitro-*p*-xylene. (*b*) 2 : 6-Dinitro-*p*-xylene. (*c*) 4 : 6-Dinitro-compound. (*d*) 2 : 4-Dinitro-compound. (*e*) 4-Nitro-compound. (*f*) 4-Sulpho-compound. (*g*) 5-Sulpho-compound. (*h*) Both values given in literature.

* Musk odour.

TABLE IV.

Polycyclic Hydrocarbons.

	M. p.	B. p.	Picrate.			Oxidation Products.	
			M. p.	Colour.	Solvent.		
1-Methylnaphthalene	—	240°	141°				
2-Methylnaphthalene	33°	240	115				
Naphthalene	80	218	150	Yellow.	Alcohol.		Nitration ⟶ α-nitronaphthalene, m. p. 61°.
1-Methylanthracene	86	—	—				
Acenaphthene	95	277	161	Orange red.	Alcohol.	Quinone, m. p. 261°; naphthalic acid.	Styphnate, m. p. 154°; orange red; alc.
Retene	99	394	123	Orange yellow.	Benzene.	Quinone, m. p. 197°.	Alc. sol. of quinone and little alc. KOH ⟶ red coloration discharged by aëration.
Phenanthrene	100	340	145	Yellow.	Alcohol.	Quinone, m. p. 203°; diphenic acid.	Sols. of pure hydrocarbon; blue fluorescence.
Fluorene	113	298	82	Red.		Fluorenone, m. p. 84°.	Violet colour in H_2SO_4; nitration ⟶ 2-nitrofluorene, m. p. 154°.
Pyrene	149	360	222	Red.	Alcohol.	Quinone, sublimes; pyrenic acid.	
2-Methylanthracene	202	—	—	Red.	Decomp. by moisture.		
Anthracene	217	351	138	Red.	Benzene.	Quinone, m. p. 280°.	Pure hydrocarbon; bluish fluorescence.
2 : 6-Dimethylanthracene	243	—	—				
Chrysene	250	448	—	Red.		Quinone, m. p. 235°.	Pure hydrocarbon; red-violet fluorescence; quinone in H_2SO_4 ⟶ blue.
Perylene	265	—	—			Quinone, d>350°, then decomp.	Sols., blue fluorescence.
Picene	350	>500	—			Quinone.	Blue fluorescence.

CHAPTER III

HYDROXY-COMPOUNDS, THIOL COMPOUNDS, ETHERS, AND THIOETHERS.

- (1) General Reactions of Hydroxy-Compounds.
    - (*a*) Formation of Metal Derivatives.
    - (*b*) Formation of Ethers.
    - (*c*) Formation of Acyl Derivatives.
    - (*d*) Replacement of Hydroxyl by Halogen.
    - (*e*) Replacement of Hydroxyl by Amino.
- (2) Special Reactions of Alcohols.
    - (*a*) Oxidation.
    - (*b*) Elimination of the Elements of Water from Alcohols.
- (3) Special Reactions of Phenols.
    - (*a*) Formation of Nitroso-Derivatives.
    - (*b*) Formation of Nitro-Derivatives.
    - (*c*) Formation of Halogen Derivatives.
    - (*d*) Reaction with Diazo-Compounds.
    - (*e*) Introduction of Aldehyde and Keto Groups.
    - (*f*) Introduction of Carboxyl Group.
    - (*g*) Lederer–Manasse Reaction.
- (4) Enolic Compounds.
- (5) Mercaptans and Thiophenols.
- (6) Ethers,
    - (*a*) Fission.
    - (*b*) Additive Compounds.
    - (*c*) Nuclear Substitution in the Aryl Ethers.
- (7) Thioethers.

(1) *General Reactions of Hydroxy-Compounds.*

ALTHOUGH the ease with which the hydroxyl of hydroxy-substituted hydrocarbons enters into reaction depends, other things being equal, on the nature and configuration of the remainder of the molecule, nevertheless there are a number of types of reactions which are common to all hydroxy-compounds. Thus the hydrogen of the hydroxyl group can be replaced by metals, by acyl, alkyl, or aryl groups, or even the hydroxyl itself may be substituted by other groupings.

(a) *Formation of Metal Derivatives.*—Hydroxy-substituted hydrocarbons dissolve sodium with the evolution of hydrogen and the formation of metal derivatives of the type $R{\cdot}ONa$, where R is alkyl or aryl. Such compounds are obtained from the saturated aliphatic alcohols by the addition of sodium to an excess of the dry alcohol, carbon dioxide being excluded. For many purposes such solutions of the sodium alkoxide are suitable. If the alcohol-free product is required, the bulk of solvent may be removed by distillation and the residue freed from the remainder of the solvent by heating to

80—200° in a stream of dry carbon dioxide in a copper vessel. more convenient general method for the preparation of dry alkali lcoholates is to allow the finely-divided metal in an indifferent lvent to react with the requisite amount of the alcohol.

Preparation of Dry Sodium Alcoholates.—Finely-divided sodium is first repared by covering a weighed amount of the clean metal with xylene, hich has been dried by keeping in contact with sodium and distilling over e same metal.

The mixture of sodium and the dried xylene is heated until all the metal as melted. The flask, a stout round-bottomed one, is closed by a sound rk and shaken vigorously till the sodium has solidified to a suspension of e granules. It is necessary that the flask should be covered by dusters ring this operation to minimise the effect should the flask burst.

A more convenient method of obtaining the finely-divided metal is to stir e molten metal as it cools under the xylene by an efficient mechanical stirrer rühl, *Ber.*, 1904, **37**, 2066; compare *Organic Syntheses*, 1929, **9**, 38).

The dry sodium alkoxide is prepared by slowly adding the calculated nount of dry alcohol to the sodium powder, which is still suspended in the ylene. The mixture is again stirred mechanically. After the whole of the ~~odium~~ has been added, the mixture is heated under reflux till all the sodium as reacted. If necessary, the white suspension of alcoholate can be collected, recautions being taken to prevent access of moisture and carbon dioxide.

This method can also be employed for the preparation of sodium phenoxide om phenol.

The higher secondary and tertiary alcohols react comparatively lowly with sodium and do not yield alcoholates readily. In such ases potassium "emulsified" in benzene can be employed with dvantage. Thus cholesterol and ergosterol can be smoothly onverted into potassium derivatives by this method (Bose and oran, *J.*, 1929, 2246; Heilbron and Simpson, *ibid.*, 1932, 270).

The alcoholates of magnesium, calcium, and barium have been repared by reaction of the metal with the lower aliphatic alcohols. or example, calcium ethoxide is obtained by boiling calcium with large excess of dry ethyl alcohol and subsequently removing the ulk of the alcohol by distillation and completing the evaporation n a vacuum desiccator. Crystals of the composition $Ca(OEt)_2,2EtOH$ re thus obtained (F. M. Perkin and L. Pratt, *J.*, 1909, **95**, 159).

Preparation of Magnesium Ethoxide.—A suspension of 10 g. of magnesium ilings in 100 c.c. of absolute alcohol and 20 c.c. of xylene, to which a small amount of mercuric chloride and iodine have been added, is heated gently under reflux. An evolution of hydrogen commences and the filings begin o be surrounded by a distinctly crystalline mass of $Mg(OEt)_2$, which gradually increases in bulk till it fills the flask and resembles boiled rice in appearance. After heating for about 5 hours the reaction is complete. The product may then be freed from solvent by distillation or filtration. It is a colourless mass almost insoluble in water (Meerwein and R. Schmidt, *Annalen*, 1925, **444**, 236).

The alcoholates of aluminium have important practical applications (see pp. 127–130, 161) and are prepared by methods similar to that employed for the preparation of magnesium ethoxide (Gladstone and Tribe, *J.*, 1881, **39**, 1; Tischtschenko, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 355).

Preparation of Aluminium Ethoxide.—Coarse aluminium powder (100 g.) is covered by 650 c.c. of dry xylene in a flask fitted with a reflux and a dropping funnel. The xylene is heated to boiling and 440 c.c. of absolute alcohol in which 0·5 g. of mercuric chloride and of iodine, respectively, have been dissolved, are dropped into the boiling liquid. A vigorous reaction sets in, and the flask must be removed from the source of heat. Fresh alcohol is added as required. When about 330 c.c. of alcohol have been added, the flask is again heated and the rest of the alcohol added slowly. The operation requires about 1½—1¾ hours, and is generally completed by heating for a further period of ¼ hour till the evolution of hydrogen has quite ceased. It is then filtered through a hot fluted funnel to remove the excess of aluminium and the solvent distilled off under reduced pressure, leaving a residue of colourless fused aluminium ethoxide (yield 400 g.) (Meerwein and R. Schmidt, *Annalen*, 1925, **444**, 231).

Preparation of Aluminium iso*Propoxide.*—*iso*Propyl alcohol (dried over barium oxide) (300 c.c.) containing about 1 g. of mercuric chloride is poured over 25 g. of aluminium shavings and then heated under reflux till the metal is completely dissolved. (If the reaction does not start, a little iodine and copper powder should be added.) The excess of alcohol is distilled off, the residue distilled in high vacuum, and the distillate of aluminium *iso*propoxide collected in vessels which can be sealed off (Reichstein, Ammann, and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 264).

The alcoholates of calcium, barium, and lead have been prepared by double decomposition between the nitrates and sodium alkoxide in liquid ammonia (Chablay, *Compt. rend.*, 1911, **153**, 819, 953. For other methods of preparing calcium ethoxide, see Doby, *Z. anorg. Chem.*, 1903, **35**, 93).

The majority of the known alcoholates are substances insoluble in non-hydroxylic solvents and non-volatile. The alkoxides of aluminium are, however, easily soluble in benzene, and with the exception of aluminium methoxide, the lower members can be distilled unchanged under reduced pressure. According to Sidgwick and Sutton (*J.*, 1930, 1461) they can be regarded as esters of aluminic acid. The thallous alcoholates appear to be abnormal in that they dissolve in benzene and are polymerised (Sidgwick and Sutton, *loc. cit.*).

The alcoholates of the alkali metals are decomposed by water with the liberation of alcohol and the formation of the alkali hydroxide. The phenates, on the other hand, are comparatively stable in presence of water, and can be obtained in aqueous solution by dissolving the phenol in an aqueous solution of caustic alkali. Evaporation of such a solution yields the dry phenate. A more convenient method, giving a purer product, depends on the action of the alkali metal on the phenol dissolved in an inert solvent. A further method consists in the addition of the requisite amount of sodium methoxide in methyl alcohol to an alcoholic solution of the phenol. The solvent is afterwards removed in an inert atmosphere at a temperature of 100—150°.

(b) *Formation of Ethers.*—The most general method of converting a hydroxy-compound into its ether consists in allowing the metal derivative—usually the sodium salt—to react with the appropriate alkyl halide, aryl halide, or the alkyl esters of arylsulphonic acids

Purdie and Irvine, *ibid.*, p. 485; A. McKenzie, *ibid.*, p. 754; Purdie and Irvine, *J.*, 1903, **83**, 1021; Purdie and Bridgett, *loc. cit.*, p. 1037).

Since the aryl halides are comparatively unreactive, the preparation of the diaryl ethers by the action of aryl halides on metal phenates does not proceed easily. The reaction between bromobenzene and sodium phenate, for instance, requires a temperature of about 300°. The addition of a small amount of copper bronze has the effect of bringing about the reaction at a lower temperature.

Preparation of Diphenyl Ether.—Potassium phenate (prepared from 16·8 g. of phenol and 3·9 g. of potassium) is heated with 15·7 g. of bromobenzene and 0·1 g. of copper bronze at 210° for 2 hours. An excess of alkali is then added and the product distilled in steam. Fractionation of the oil driven over gives diphenyl ether, b. p. 259° (corr.); m. p. 27° (yield 14 g.).

Iodobenzene reacts similarly; with chlorobenzene sealed tubes are necessary.

Instead of preparing potassium phenate for this reaction a mixture of phenol (16·8 g.) and powdered potassium carbonate (6·9 g.) can be used.

The same method has been used successfully for the preparation of other diaryl ethers. Tolyl phenyl ether, naphthyl phenyl ether, dinaphthyl ether; *o*-, *m*-, and *p*-dibromobenzenes all react similarly, giving aryl ethers of dihydric phenols (Ullmann and Sponagel, *Ber.*, 1905, **38**, 2211; *Annalen*, 1906, **350**, 86).

Nitrohalogen benzenes react more easily than the unsubstituted aryl halides. Provided that a nitro-group is *ortho* or *para* to the halogen it is not necessary to use copper bronze as catalyst. The following general method has been described by Fox and E. E. Turner (*J.*, 1930, 1119).

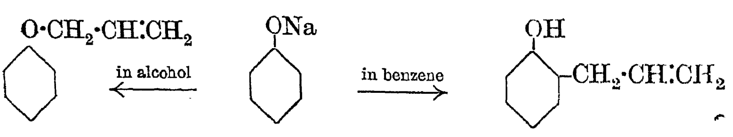
Preparation of Nitrodiaryl Ethers.—Potassium hydroxide (1 mol. prop.) is treated with sufficient water (about 0·06—0·1 mol. prop.) so that a clear solution is obtained at about 250°. The solution thus obtained is cooled till it commences to crystallise, when 1 mol. prop. of the phenol is added rapidly and the mixture stirred.

If it is desired to prepare mononitro-ethers from compounds like *o*-nitrochlorobenzene or 2 : 5-dibromonitrobenzene, the appropriate nitro-halogen compound (1 mol. prop.) is added in one quantity to the still hot phenoxide solution. After a thorough mixing, the product is heated under a short air condenser at 160—180° for 3—4 hours.

If 2 : 4-dinitrochlorobenzene is used, the nitro-compound is added with vigorous shaking during 5 minutes and the reaction completed by heating at 100° for 1 hour.

In all preparations the reaction product is shaken with hot dilute alkali, and the cooled mixture filtered or extracted with ether.

The solvent itself may have an important influence on the course of the etherification of phenols. This is particularly so with allyl bromide, cinnamyl bromide, and the benzyl halides. These halogen compounds react with the dry alkali phenates in non-dissociating solvents such as benzene or toluene to give nuclear-substituted phenols. In methyl alcohol and similar solvents the normal ether is formed (Claisen, Kremers, Roth, and Tietze, *Annalen*, 1925, **442**, 210).



Preparation of 2-Benzyl-1-hydroxynaphthalene.—The dry sodium salt of α-naphthol is prepared by the action of 4·6 g. of sodium wire on 29 g. of α-naphthol in 100 g. of toluene. A hot paste of the sodium salt results, to which are added 26 g. of benzyl chloride. After the spontaneous reaction has moderated, the mixture is heated in an oil bath so that it gently boils for several hours. On cooling, water is added, the toluene layer removed and evaporated under reduced pressure to remove the solvent. The residue is covered with several volumes of methyl alcoholic potash and the insoluble matter extracted with light petroleum. Several extractions are necessary. The phenol liberated from the alkaline solution is taken up in ether and distilled under reduced pressure. At 235—245°/12—13 mm. 26 g. of a thick oil are obtained, which gradually solidifies. After draining on a porous tile and subsequently crystallising first from hot light petroleum (b. p. 60—80°) and then from a mixture of acetic acid and 85% formic acid, the pure product results, m. p. 74°.

A somewhat similar process may be used for the preparation of *o*-allyl phenol and *o*-allyl *p*-cresol, for *o*-benzyl phenol and benzyl *p*-cresol and *o*-cinnamyl phenol. The group enters the position *ortho* to the hydroxyl.

Nuclear substitution during the etherification of some di- and tri-hydric phenols—particularly when the hydroxyls are *meta* to one another—has been observed, but the conditions are not quite analogous to those described for the monohydric phenols (Herzig and Zeisel, *Monatsh.*, 1889, **9**, 882; **10**, 144; 1890, **11**, 291; Hirschel, *ibid.*, 1902, **23**, 181; Kaufler, *ibid.*, 1900, **21**, 993; Ott and Nauen, *Ber.*, 1922, **55**, 924).

In the preparation of the methyl ethers of phenolic substances, dimethyl sulphate finds a considerable application. The general procedure is to shake the phenol in aqueous alkaline solution with slightly more than the necessary amount of dimethyl sulphate.

Preparation of Anisole.—47 G. of phenol and 20 g. of sodium hydroxide in 200 c.c. of water are mixed in a litre flask fitted with a stirrer and condenser. The mixture is cooled to below 0° and 63 g. of dimethyl sulphate are added gradually from a dropping funnel. When all has been added the flask is heated on a water-bath, and after about ½ hour a further amount of 47 g. dimethyl sulphate and 20 g. of sodium hydroxide in 200 c.c. of water is added. The mixture is then refluxed vigorously for 10—15 hours. On cooling, the anisole is separated, washed with water, dried, and distilled; it is collected at 153—154°—yield 60—75% of theory (Hiers and Hager, *Organic Syntheses*, 1929, **9**, 12).

In this preparation the amount of dimethyl sulphate is only sufficient for the utilisation of one of the methyl groups. This is evident from the following equation:—

$$C_6H_5ONa + (Me)_2SO_4 \qquad C_6H_5OMe + Na(Me)SO_4$$

✓ *Preparation of Veratrole.*—A solution of 100 g. of catechol in 200 c.c. of methyl alcohol is mixed with 250 g. of dimethyl sulphate. After cooling to −5°, a solution of 150 g. of caustic potash in 350 c.c. of water is added all at once. A vigorous reaction takes place and the methylation is complete in about 3 minutes. The resulting mixture is diluted with water, the oil extracted with ether, the ethereal layer washed and then dried over calcium chloride. After evaporation of the solvent, the residue is distilled. Yield of veratrole, m. p. 15°, b. p. 205°, 95% of theory (W. H. Perkin, jun., and Weizman, *J.*, 1906, **89**, 1649).

When the alkylation does not proceed readily in aqueous solution, as with the *o*-nitrophenols and some of the polyhydroxyanthraquinones, the dry salt of the phenol should be heated with dimethyl sulphate to between 110° and 160° (Graebe and Aders, *Annalen*, 1901, **318**, 367; Ullmann, *ibid.*, 1903, **327**, 114; O. Fischer and Gross, *J. pr. Chem.*, 1911, [ii], **84**, 371).

Preparation of o-*Nitroanisole.*—A mixture of 30 g. of the dry sodium salt of *o*-nitrophenol, 10 c.c. of toluene, and 24 g. of freshly distilled dimethyl sulphate is stirred mechanically and heated in an oil bath at 110—120° till the orange colour disappears. The mixture is diluted with water, made alkaline, and after boiling, the *o*-nitroanisole is extracted with ether. Yield, 26 g. (Ullmann, *loc. cit.*).

The application of dimethyl sulphate to the methylation of aliphatic hydroxy-compounds has been examined by W. N. Haworth (*J.*, 1915, **107**, 8), and has since been employed in the preparation of methylated sugars. Its application in this field has greatly facilitated the investigation of the structure of the di- and trisaccharides. For examples of its use in this direction the original papers of Haworth and his pupils should be consulted (*J.*, 1915—1932).

The alkali salts of the methyl and ethyl hydrogen sulphates have been used for the alkylation of phenols, but apparently it is necessary to use temperatures of the order of 150° and sealed vessels (Graebe, *Annalen*, 1905, **340**, 208; Witt and Schneider, *Ber.*, 1911, **34**, 3173).

An elegant method for the preparation of the ethers of triphenylmethane consists in acting upon triphenylmethyl chloride with the appropriate hydroxy-compound in pyridine solution. The process has been applied to the simple alcohols, to hydroxy esters, and to sugars (Helferich, Speidel, and Toeldte, *Ber.*, 1923, **56**, 766; Helferich, Moog, and Jünger, *ibid.*, 1925, **58**, 872).

Diazomethane has been employed for the methylation of the phenolic hydroxy-group. Alcohols appear to be indifferent, or almost indifferent, to this reagent. For examples of this method see papers by E. Fischer and Freudenberg (*Ber.*, 1913, **46**, 1123), Fischer and Hoesch (*Annalen*, 1912, **391**, 351), and von Pechmann (*Ber.*, 1895, **28**, 857; 1898, **31**, 501).

The lower saturated aliphatic alcohols can be converted into the corresponding ethers by the action of warm sulphuric acid under suitably controlled conditions. For the preparation of diethyl ether, ethyl alcohol is added slowly and regularly to a mixture of equal weights of concentrated sulphuric acid and ethyl alcohol maintained at 140°. The addition of about 5—10% of anhydrous aluminium sulphate brings about the formation of the ether at a lower temperature (Senderens, *Compt. rend.*, 1910, **151**, 3925; compare Schlatter, *J. Ind. Eng. Chem.*, 1920, **12**, 1101). A similar process can be used for the preparation of di-*n*-propyl ether. For the production of ethers from the higher alcohols, these conditions require modification in order to prevent undue formation of olefin and to minimise other side reactions. It is usual to use only a small proportion of sulphuric acid and subsequently to separate the ether formed from the olefin by fractionation (compare the preparation of amylene, p. 90).

This method of ether formation is generally regarded as involving the reaction of the alcohol with the alkyl hydrogen sulphate according to the scheme:

$$\mathrm{R{\cdot}OSO_2{\cdot}OH + ROH \qquad R_2O + H_2SO_4}$$

The sulphuric acid in this reaction may be replaced by aryl sulphonacids or even their esters.

This type of reaction has been applied to the preparation of mixed ethers, although the success of the process depends apparently on the choice of suitable hydroxy-compounds. Thus, while mixtures of ethyl and propyl alcohols furnish some mixed ether by this method (Norton and Prescott, *Amer. Chem. J.*, 1884, **6**, 245), the reaction of *tert.*-butyl alcohol with primary aliphatic alcohols in presence of aqueous sulphuric acid gives good yields of *tert.*-butyl alkyl ethers (J. F. Norris and Rigby, *J. Amer. Chem. Soc.*, 1932, **54**, 2095).

In some preparations the sulphuric acid may be replaced by hydrogen chloride, as in the formation of the methyl or ethyl ethers of benzoin. This is effected by keeping at 40° solutions of benzoin in the appropriate alcohol saturated with hydrogen chloride. The reaction is similar to the formation of glucosides from monosaccharides (E. Fischer, *Ber.*, 1893, **26**, 2400, 2412).

A somewhat similar process can be used for the preparation of certain aryl alkyl ethers. Thus α- and β-naphthols, α- and β-anthranols, phenanthranol, and some dihydroxyanthracenes yield ethyl and methyl ethers by heating with the appropriate alcohol and sulphuric acid or hydrogen chloride (Liebermann and Hagen, *Ber.*, 1882, **15**, 1427; Gattermann, *Annalen*, 1888, **244**, 72; Findlay and Japp, *J.*, 1897, **71**, 1122; Lampe, *Ber.*, 1909, **42**, 1416). Mono- and di-hydroxybenzenes do not appear to furnish ethers by this method. Phloroglucinol, however, is an exception, for it can be partially methylated by treatment with hydrogen chloride in methyl alcohol (Weidel and Pollak, *Monatsh.*, 1900, **21**, 22; Freudenberg, *Ber.*, 1920, **53**, 1425; D. D. Pratt and Robinson, *J.*, 1924, **125**, 193).

It is noteworthy that carbinols containing the grouping $-\overset{|}{\mathrm{N}}{\cdot}\underset{|}{\overset{|}{\mathrm{C}}}(\mathrm{OH})$, such as cotarnine, berbinol, and the simple additive compounds of formaldehyde with primary and secondary aliphatic amines, form the corresponding ethers simply by treatment with the appropriate alcohol (G. M. Robinson and Robinson, *J.*, 1917, **111**, 967; 1923, **123**, 532; McLeod and G. M. Robinson, *ibid.*, 1921, **119**, 1470).

(c) *Formation of Acyl Derivatives.*—The replacement of the hydrogen of the hydroxy-group by acyl groups to yield esters can generally be effected by means of an acid anhydride or acyl chloride under suitable conditions. The free carboxylic acids can also be used, but their application is determined by the nature of the hydroxy-compound. Primary and secondary alcohols in general yield esters comparatively easily. The esters of tertiary alcohols and phenols are not prepared by this method.

(1) *From Acyl Halides and Anhydrides.*—The simple alcohols react with acyl anhydrides to yield esters according to the scheme

$$R{\cdot}OH + O(OC{\cdot}R')_2 \longrightarrow R{\cdot}O{\cdot}CO{\cdot}R' + R'{\cdot}CO_2H$$

This reaction can be brought about quite simply by warming together approximately equimolecular proportions of the reactants and subsequently removing the acid by treatment either with water or with dilute sodium carbonate solution or by fractionation. The cyclic anhydrides of the dibasic acids behave similarly to give acid esters (see p. 231).

With phenols and other hydroxy-compounds, acylation is effected by heating with the anhydride after adding some fused sodium salt. Under special circumstances to effect a similar acylation, other substances, such as zinc chloride, small amounts of sulphuric acid, perchloric acid, thionyl chloride, or sulphuryl chloride, may be necessary.

Preparation of Quinol Diacetate.—Quinol is heated on a steam-bath for ½ hour with about six times its weight of acetic anhydride and about ¼ its weight of fused sodium acetate. The reaction mixture is then poured into water, and after the excess of anhydride has been destroyed, the acetate is collected and washed with water. It is purified by crystallisation from alcohol, m. p. 122°.

The acetates of other phenols can be prepared similarly.

Preparation of β-Glucose Pentacetate.—200 G. of anhydrous glucose and 100 g. of finely-powdered anhydrous sodium acetate are mixed in a 3-l. flask and heated in a water-bath with 1000 g. of acetic anhydride. The mixture should be stirred continuously till a clear solution is obtained. The acetylation is completed by heating for a further period of 2 hours, when the solution is poured in a thin stream into 4 l. of ice water agitated by an efficient stirrer. The pentacetyl glucose separates as a crystalline mass, and is collected after keeping for several hours. It is then ground in a mortar with water and kept until the anhydride is completely hydrolysed. Finally it is collected and purified by crystallisation from 1 l. of hot alcohol (96%)—yield, 300—330 g. (E. Fischer, *Ber.*, 1916, **49**, 584).

An effective and simple method of acetylating phenols has recently been described by Chattaway (*J.*, 1931, 2495). The general process consists in dissolving the phenol in an aqueous solution of little more than the theoretical amount of sodium or potassium hydroxide, diluting with a suitable quantity of crushed ice, and then adding slightly more than the requisite amount of acetic anhydride. After shaking for a few moments, the acetyl derivative separates in a practically pure condition. By this process phenyl acetate is obtained from phenol in 98% yield. Di- and tri-hydroxyphenols, nitro- and halogen-substituted phenols, and esters of phenolic acids are similarly acetylated. Although salicylic acid does not give an acetyl derivative by this method, *p*-hydroxybenzoic acid and gallic acid give good yields. In acetylating these acids the solution must be acidified after the reaction in order to liberate the acetylated acid.

The use of acyl chlorides for the preparation of esters is of wide application. The alcohols, in general, react quite readily with acid chlorides, hydrogen chloride being eliminated. Indeed, in the case of acetyl chloride, it is advisable to cool the mixture so as to moderate the reaction, especially if volatile alcohols are used. With benzoyl chloride and other acyl chlorides, which are comparatively stable to water and cold aqueous alkali, the reaction may be brought about either by warming an excess of the alcohol with the acyl chloride and then distilling off the excess of alcohol when the reaction is complete, or more conveniently, if the alcohol is not easily volatile, a slight excess of the chloride in presence of dilute sodium hydroxide solution may be used. This latter method is well suited for the preparation of the phenyl esters of the aromatic acids.

*Preparation of Methyl-*p*-nitrobenzoate.*—0·1 G. of *p*-nitrobenzoyl chloride is gently boiled in an ignition tube with 0·5 c.c. of methyl alcohol. After 3 or 4 minutes, the solution is poured on a watch-glass and the excess of alcohol allowed to evaporate. The crystalline ester is washed with a small quantity of dilute sodium carbonate solution, then water, and finally crystallised from aqueous alcohol.

The ethyl and propyl esters are prepared similarly. Instead of *p*-nitrobenzoyl chloride, 3 : 5-dinitrobenzoyl chloride or other substituted benzoyl chlorides may be similarly employed.

*Preparation of Benzyl-*p*-nitrobenzoate.*—*p*-Nitrobenzoyl chloride in slight excess (0·1 g.), the alcohol (0·05 g.), and 2 drops of 20% sodium hydroxide solution are mixed and shaken, warmed very gently, till the solid ester separates. It is collected, and after washing with water, is crystallised from aqueous alcohol.

Preparation of Phenylbenzoate.—To a solution of 1 g. of phenol in 5 c.c. of water and 5 c.c. of 20% sodium hydroxide solution is added about 1 c.c. of benzoyl chloride drop by drop, shaking the mixture vigorously after the addition of each portion of the acyl chloride. As soon as all the benzoyl chloride has reacted, the ester is collected, washed with dilute sodium hydroxide solution and water. It is finally dried and crystallised from alcohol.

This method is a general one for the preparation of the esters of phenols from such acyl halides as are not easily hydrolysed by water and dilute alkali, *e.g.* benzoyl chloride and its homologues, or aryl sulphonyl chlorides.

A very useful method for acylating hydroxyl groups consists in the reaction of the hydroxy-compound with the appropriate acid chloride or anhydride in presence of pyridine, quinoline, or less rarely some other tertiary amine. The general method of procedure is to add the acid chloride or anhydride to a well-cooled solution of the alcohol or phenol in about 5 times its weight of pyridine. After keeping at room temperature for several hours, the reaction mixture, which has usually developed a dark red colour, is poured into dilute acid containing lumps of ice. The acyl derivative is thrown down either as a solid or as an oil. It is taken up in ether or chloroform and the resulting solution washed with dilute acid till free from pyridine. When the acid chloride is derived from a sparingly soluble acid, this must be removed from the solution by washing with dilute sodium carbonate solution (Einhorn and Hollandt, *Annalen*, 1898, **301**, 95).

This process is widely used for the acylation of such hydroxy-compounds as polyhydric alcohols, sugars, phenols, etc. The following modification is recommended by Reichstein (*Helv. Chim. Acta*, 1926, **9**, 800) as suitable for the characterisation of small amounts of alcohols and phenols.

Preparation of 3 : 5-*Dinitrobenzoic Esters for the Characterisation of Alcohols and Phenols.*—A few drops of the alcohol or a small amount of the phenol dissolved in benzene is mixed with a solution of 3 : 5-dinitrobenzoyl chloride in benzene and some pyridine added.

After keeping for some hours at room temperature (with *tert.*-alcohols it is necessary to heat to boiling point for ½ hour), the reaction mixture is diluted with dry ether, washed in a separating funnel with dilute hydrochloric acid, then with dilute sodium hydroxide, and finally with a large volume of water. Evaporation of the ethereal solution, followed by warming under reduced pressure, yields the pure ester.

Phenols and polyhydric alcohols give principally esters which are sparingly soluble in organic solvents. In such cases it is sufficient to filter off the product after washing with water.

Preparation of Esters of Anthraquinone-β-carboxylic Acid.—A few drops of the dry alcohol are mixed with an excess of chloride of anthraquinone β-carboxylic acid, dissolved in benzene. The mixture is diluted with ether and an excess of dry pyridine added. After keeping in a closed vessel for some hours, the mixture is filtered, and the insoluble residue washed with ether. The filtrate and washings are combined, washed with dilute hydrochloric acid, then with about 1 c.c. of 50% aqueous potassium hydroxide solution, and finally shaken mechanically with 1 c.c. of 50% aqueous potassium hydroxide solution. Evaporation of the ethereal solution yields the crystalline ester.

The use of chlorocarbonic esters for acylation is of special application to phenolcarboxylic acids, for by protecting the phenolic hydroxyl groups by methyl carbonate groups, the carboxyl group can be converted smoothly into –COCl by the action of phosphorus halides :

$$HO{\cdot}C_6H_4CO_2H + Cl{\cdot}CO{\cdot}OCH_3 \longrightarrow CH_3{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2H + HCl$$

The following are examples of the application of chlorocarbonic esters :

Preparation of Methyl Carbonate of p-*Hydroxybenzoic Acid,*

$CH_3{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2H$.

—To a well-cooled solution of 5 g. of *p*-hydroxybenzoic acid in 64 c.c. of *N*-sodium hydroxide solution (2 mol. props.), add gradually 3·8 g. of methyl chlorocarbonate in 2 or 3 portions. The greater part of the chloride goes into solution immediately, but the excess is hydrolysed slowly. The solution is finally acidified with dilute hydrochloric acid, and the voluminous precipitate thus thrown down is drained and dried on a porous tile. It is purified by adding water gradually to a hot acetone solution till a turbidity results. On slow cooling the methyl carbonate separates in small fine needles, m. p. 179°, yield quantitative (E. Fischer, *Ber.*, 1908, **41**, 2877).

The method described above can be applied to the preparation of alkyl carbonates of other phenolic acids. If there is a hydroxyl group *ortho* to the carboxyl, the following method is advisable.

Preparation of Methyl Carbonate of Salicylic Acid.—Salicylic acid (50 g.) and dimethylaniline (88 g.) are mixed in 250 c.c. of dry benzene, and to the solution 34·3 g. of methyl chlorocarbonate are added over a period of ¾ hour, with constant shaking. Just before the addition of each fresh portion of the chlorocarbonate, the solution is cooled in a freezing mixture till the benzene solidifies. When all the chloride has been added and its odour has disappeared, an excess of hydrochloric acid is added, and the benzene layer separated. The carbomethoxy-compound soon separates from the benzene, and after the separation is complete, the precipitate is collected and washed with cold benzene and water. It is then dried on a tile, triturated with water, washed with water, and finally dried in a vacuum desiccator. It is purified by crystallisation from 4 times its weight of ethyl acetate by the addition of light petroleum, m. p. 135°, yield 60%.

(2) *By Reaction with Acids.*—Carboxylic acids are able to react directly with the hydroxyl group to yield acyl derivatives according to the scheme :

$$R{\cdot}CO_2H + HO{\cdot}R' \longrightarrow R{\cdot}CO_2R' + H_2O.$$

The ease with which esterification takes place is determined largely by the type of hydroxy-compound and by the acid used. For the effect of the type of alcohol on the formation of acetates by heating with acetic acid, reference should be made to the following papers : Menschutkin, *Annalen*, 1879, **195**, 334; *Ber.*, 1909, **42**, 4020; Willstätter and Hocheder, *Annalen*, 1907, **354**, 249; Willstätter, E. W. Mayer, and Hüni, *ibid.*, 1910, **378**, 98; Michael, *Ber.*, 1910, **43**, 464; Michael and Wolgast, *ibid.*, 1909, **42**, 3157. Gandurin, *ibid.*, 1908, **41**, 4360.

In general, it may be said that primary alcohols react more readily than the corresponding secondary alcohols, while tertiary alcohols and phenols do not react to any serious extent. The preparation of acyl derivatives by the direct action of a carboxylic acid on an alcohol is restricted, therefore, for all practical purposes, to primary and secondary alcohols. Except in special circumstances, the preparation of esters by this method is effected by warming a solution of the acid in an excess of the appropriate alcohol using as a catalyst a little sulphuric acid or alcohol containing hydrogen chloride. The amount of catalyst need be only about 1—5% of the weight of alcohol used. The product is isolated by distilling off most of the alcohol, pouring the residue into water, and neutralising it by the addition of sodium carbonate solution. After separation of the ester from the aqueous layer it is dried and fractionated. If the ester is soluble in water, it is more convenient to neutralise the acid first by the addition of finely-powdered potassium carbonate, then dilute with ether, filter, and fractionate under reduced pressure. The homologues of formic acid, the aromatic acids, many hydroxy acids such as lactic and glycollic acids, as well as dibasic acids, can be esterified by this method (E. Fischer and Speier, *Ber.*, 1895, **28**, 3252). Even some unsaturated acids such as cinnamic and crotonic give esters under these conditions.

Those carboxylic acids which are sensitive to mineral acids are esterified by special methods. Thus pyruvic acid and similar acids are converted into esters by heating with the appropriate alcohol at 100° in a sealed tube. Oxalic esters are prepared simply by heating the anhydrous acid with the alcohol under reflux and subsequently fractionating the product.

Instead of acids as catalysts for esterification, some metal sulphates have been employed (Bogojavlenski and Narbutt, *Ber.*, 1905, 38, 3344). Of these, it appears that copper sulphate dehydrated at a comparatively low temperature can be used with advantage for the esterification of α-hydroxy fatty acids (Clemmensen and Heitmann, *Amer. Chem. J.*, 1909, 42, 319).

An ingenious apparatus for the esterification of α-hydroxy-acids has been described by Frankland and Aston (*J.*, 1901, **79**, 517), and recently several slight modifications of this apparatus have been introduced (compare Kenyon, *Organic Syntheses*, 1925, **5**, 60). The

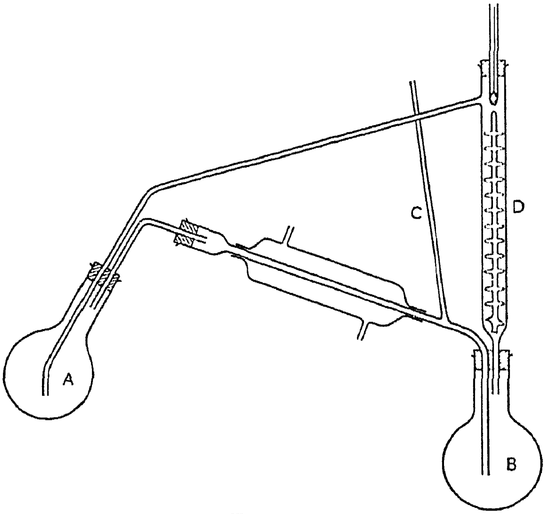


FIG. 3.

apparatus, Fig. 3, consists essentially of a flask [*A*] containing tartaric acid or some other acid covered by absolute alcohol, and heated in an oil-bath at 130°. The alcohol slowly distils through a condenser into a second flask [*B*] containing anhydrous potassium carbonate and fitted with a fractionating column connected to the first flask through a condenser. By heating the second flask, the condensed alcohol is returned, deprived of its water, through the fractionating column [*D*] to the acid in the flask [*A*]. There is thus a constant circulation of the alcohol between the acid and the drying agent. A safety-tube *C* must be provided to prevent any increase in pressure in the apparatus, and the tubes delivering the condensed alcohol should dip below the level of the liquid in each flask. When the operation is complete, the product is transferred to a distillation flask and fractionated under reduced pressure. *p*-Toluenesulphinic acid has also been esterified by this method (Houssa, Kenyon, and H. Phillips, *J.*, 1929, 1707). An interesting modification of this process takes advantage of the fact that some ternary mixtures containing water and ethyl alcohol distil at comparatively low temperatures and can be used to remove the water continuously from the esterification mixture. A process employing this principle has been described by H. T. Clarke and Davis (*Organic Syntheses*, 1922, **2**, 23) for ethyl oxalate and by McDermott (*ibid.*, 1930, **10**, 88) for *iso*propyl lactate.

Thielepape (*Ber.*, 1933, **66**, 1454) has recently described an apparatus for esterification in which the water produced in the reaction is removed by calcium carbide.

Some alcohols cannot be esterified to any serious extent by reaction with acids. Their esters must therefore be prepared by special methods.

(d) *Replacement of Hydroxyl Group by Halogen.*—The reaction of phosphorus halides with hydroxy-compounds is a general reaction whereby the hydroxyl group is replaced by halogen. Its application as a method for the preparation of alkyl and aryl halides from alcohols and phenols is, however, restricted, since the product may contain serious amounts of undesirable by-products. Thus in the reaction of phosphorus trichloride with the lower primary and secondary alcohols, the yield of alkyl chloride is rarely more than 50% of the theoretical, and usually much lower. With tertiary alcohols, however, the yields are better. More satisfactory results are obtained if zinc chloride is added to the reaction mixture (Clark and Streight, *Trans. Roy. Soc. Canada*, 1929, **23**, 77).

The replacement of the hydroxyl group of the simple phenols by treatment with phosphorus chlorides and bromides does not proceed smoothly, and usually only a comparatively small proportion of the phenol is converted into aryl chloride (compare Riche, *Annalen*, 1862, **121**, 357; Beilstein and Kurbatow, *ibid.*, 1875, **176**, 33; Autenrieth and Geyer, *Ber.*, 1908, **41**, 146). The replacement is facilitated by the presence of nitro-groups in the nucleus (see p. 56). It is noteworthy that the reaction of β-naphthol with chlorides and bromides of phosphorus has been employed as a convenient method for the preparation of β-halogen derivatives of naphthalene (Michaelis, *Annalen*, 1902, **321**, 246 *footnote*; Darzens and Berger, *Compt. rend.*, 1909, **148**, 787; compare O. Brunel, *Ber.*, 1884, **17**, 1179).

In contrast to their behaviour towards the chlorides and bromides of phosphorus, the alcohols react smoothly with phosphorus and iodine to give alkyl iodides. This reaction has been widely applied for purposes of preparation.

Preparation of Alkyl Iodides.—The dry alcohol is mixed with 0·35 atomic proportion of dried red phosphorus, and then powdered iodine is added gradually till approximately 1 atomic proportion has been reached. With methyl and ethyl alcohols the amount of alcohol taken is usually in excess of the proportion just given, but as these alcohols are soluble in water, there is no difficulty in removing them from the product. The reaction is vigorous and should be checked by cooling at suitable intervals. When all the iodine has been added the formation of iodide is completed by heating on a water-bath for 2 or 3 hours. The higher alcohols react more sluggishly, and it is necessary to keep the mixture warm during the addition of the iodine. The reaction is completed as before by heating on a water-bath or in an oil-bath. The product is isolated by distillation if the iodide has a low boiling point. Alternatively it is filtered through glass wool, washed with dilute sodium hydroxide solution till free from iodine, then dried and fractionated.

Thionyl chloride has been frequently employed for the replacement of alcoholic hydroxyl by chlorine (A. McKenzie and Clough, *J.*, 1913, **103**, 698; A. McKenzie and Tudthorpe, *J. Biol. Chem.*, 1924, **62**, 551). The actual experimental conditions appear to depend on the alcohol employed. The lower primary and secondary alcohols yield the chloride best by reaction with thionyl chloride in presence of pyridine or dimethyl- or diethyl-aniline (Darzens, *Compt. rend.*, 1911, **152**, 1314, 1601). For the higher alcohols these conditions are usually not satisfactory. They give better results by reaction with thionyl chloride alone or when it is diluted with benzene (Clark and Streight, *loc. cit.*).

The monohydric alcohols react more or less readily with halogen hydride to give alkyl halides, the hydroxyl group being replaced by halogen according to the scheme

$$R{\cdot}OH + HX \longrightarrow R{\cdot}X + H_2O.$$

The reaction conforms in type to the ordinary process of esterification. It should be noted, however, that while organic acids esterify primary alcohols most readily and tertiary alcohols only with difficulty, the reverse holds good with the reaction with halogen hydrides. For example, the tertiary aliphatic alcohols give the corresponding alkyl bromide by reaction with 48% hydrobromic acid in the cold, secondary alcohols do so on warming, while the primary alcohols yield the bromide but slowly (Kamm and Marvel, *J. Amer. Chem. Soc.*, 1920, **42**, 299). Lucas (*J. Amer. Chem. Soc.*, 1930, **52**, 802) has proposed a qualitative test for distinguishing the three types of alcohols based on these differences in reactivity.

Lucas's Test for Type of Alcohol.—The reagent is prepared by dissolving 136 g. of zinc chloride in 105 g. of concentrated hydrochloric acid. The reagent (12 c.c.) is added to 2 c.c. of the alcohol in a test tube at 26—27°. The test tube is corked and shaken. Tertiary alcohols react so rapidly that the separation of the insoluble chloride is observed from the time of mixing. Secondary alcohols give a separation of the chloride within 5 minutes. All other alcohols, provided that they are lower than hexyl, are soluble in the reagent.

Although this test can be modified for the preparation of *tert.*-alkyl chloride in reasonably large quantities, these halides are best prepared by saturating the alcohol with the dry halogen hydride.

Preparation of n-*Butyl Chloride.*—Anhydrous zinc chloride (272 g., 2 mols.) is added to 190 g. of cold concentrated hydrochloric acid (2 mols.) and to this solution 74 g. of *n*-butyl alcohol (1 mol.) are added. The mixture is refluxed vigorously over a free flame for about 4 hours. The upper layer, consisting of crude butyl chloride, is separated and gently refluxed with an equal volume of concentrated sulphuric acid for $\frac{1}{2}$ hour in a tilted distillation flask having the side arm closed by a tight cork. The chloride is then distilled from the acid, washed with water, dried, and distilled. Yield about 60 g., b. p. 76—78°.

The process has been applied to the preparation of *n*-propyl chloride, *iso*propyl chloride, *sec.*-butyl and *sec.*-amyl chlorides. The yields are between 55% and 75% of theory. With larger quantities longer periods of heating are required (J. F. Norris, *Organic Syntheses*, 1925, **5**, 27).

Preparation of tert.*-Butyl Iodide.*—A stream of dry hydrogen iodide (for preparation see Bannow, *Ber.*, 1874, **7**, 1498) is led into dry *tert.*-butyl alcohol. This results in the generation of a considerable amount of heat, and it is advisable to moderate the reaction by external cooling. The alcohol should also be shaken continuously during the saturation. The completion of the reaction is shown by the separation into two layers. The upper one, consisting of *tert.*-butyl iodide if the saturation has been complete, is removed, washed with a little ice-cold water, dried in contact with anhydrous sodium sulphate, and then distilled, b. p. 100°.

The preparation of other *tert.*-alkyl iodides is achieved in the same way.

(e) *Replacement of the Hydroxyl by Amino.*—The direct replacement of the hydroxyl of alcohols and of phenol and its homologues by amino has long been known to require drastic conditions. Thus ethyl alcohol yields a mixture of mono-, di-, and tri-ethylamines when it is heated with ammonium halides at 350—360° (Berthelot, *Jahresb.*, 1852, 551; Morgan and D. D. Pratt, *J.S.C.I.*, 1932, **51**, 283T). Phenols under similar conditions are converted into a mixture of primary and secondary arylamines. Thus *m*-5-xylenol gives a 20% yield of *m*-5-xylidine and a 30% yield of di-*m*-xylylamine when it is heated with half its weight of ammonium chloride for 2 hours at 350°. A similar yield of primary base with only a trace of secondary amine results by heating with ammonia at 350° for 8 hours (Morgan and Pratt, *loc. cit.*; compare Laurent, *J. pr. Chem.*, 1844, [i], **32**, 286). The replacement of the hydroxyl group of phenols has also been effected by heating with ammonia and suitable metal chlorides or with aluminium hydroxide (Imperial Chemical Industries, E.P. 355,715; I. G. Farbenind., E.P. 368,373).

The replacement of the hydroxyl of alcohols and phenols has been effected largely by heating with the additive compound of zinc chloride and ammonia. Thus ethyl or methyl alcohols are converted into a mixture of primary, secondary, and tertiary amines by heating at about 300° with ammonia zinc chloride (Merz and Gasiorowski, *Ber.*, 1884, **17**, 623). Phenols under similar conditions yield primary and secondary arylamines (Merz and Weith, *Ber.*, 1880, **13**, 1298; Merz and P. Müller, *ibid.*, 1886, **19**, 2901; Buch, *ibid.*, 1884, **17**, 2635), while if the ammonia zinc chloride is replaced by the zincichlorides of primary arylamines, diarylamines are formed. Phenol furnishes a mixture of aniline and diphenylamine when heated with ammonia zinc chloride at 300°; diphenylamine is formed if it is heated with aniline zincichloride.

Such replacements take place much more readily with nitrosophenols (O. Fischer and E. Hepp, *Ber.*, 1887, **20**, 2475) and with the naphthols (Bucherer, *J. pr. Chem.*, 1905, [ii], **71**, 433; Bucherer and Seyde, *ibid.*, 1907, [ii], **75**, 249).

Preparation of β-Naphthylamine from β-Naphthol.—A mixture of 100 g. of β-naphthol, 150 c.c. of 40% aqueous solution of sodium sulphite, and 100 c.c. of 20% aqueous ammonia is heated at 100—150° in an autoclave fitted with a stirrer. The insoluble β-naphthylamine is filtered from the product and washed with dilute sodium hydroxide to remove traces of unchanged β-naphthol. The yield is almost quantitative.

Under similar conditions resorcinol gives *m*-phenylenediamine (Bucherer, *loc. cit.*).

(2) *Special Reactions of Alcohols.*

(a) *Oxidation.*—The group $-CH_2 \cdot OH$ which is characteristic of the primary alcohols can be oxidised successively to $-CHO$ and then $-CO_2H$. The secondary alcohols—containing the group $>CH \cdot OH$—yield ketones on oxidation; tertiary alcohols are broken down to compounds containing fewer carbon atoms.

The conversion of the simple aliphatic alcohols into the corresponding aldehydes can be achieved by the action of dichromate and diluted sulphuric acid or manganese dioxide and sulphuric acid. These general methods have been used for a considerable time (compare Liebig, *Annalen*, 1835, **14**, 133). They have the disadvantage that the aldehydes may suffer further oxidation to the corresponding acids with the consequent diminution of yield. For the preparation of acetaldehyde from ethyl alcohol, the original method of oxidation by acidified dichromate has been modified with good results by introducing a stream of carbon dioxide in order to remove the volatile aldehyde as fast as it is formed.

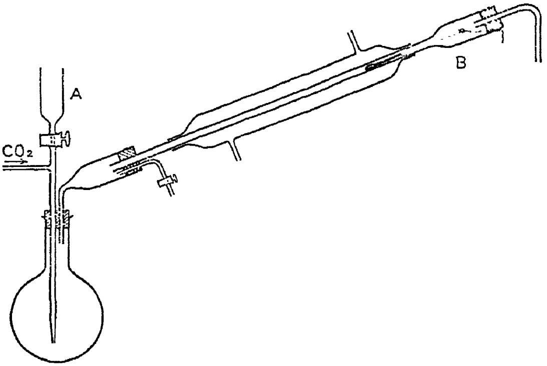


Fig. 4.

Preparation of Acetaldehyde.—This preparation is effected in the apparatus represented diagrammatically (Fig. 4). Ethyl alcohol (25 c.c.) is heated to boiling by means of a small flame, and the oxidising solution added from the funnel *A* at such a rate that the thermometer *B* suspended in the condenser reads 20—25°. The addition of the oxidising mixture usually requires about 20 minutes. Throughout the operation a stream of carbon dioxide is passed through the reaction mixture to remove the volatile aldehyde as fast as it is formed. The aldehyde is collected in bottles cooled in a freezing mixture. The first bottle contains 150 c.c. of dry ether; the second 125 c.c. of the same solvent.

The aldehyde which is collected in the ether is precipitated as aldehyde ammonia by passing dry ammonia through the ethereal solutions when the oxidation is complete—yield of dry acetaldehyde ammonia corresponds with a 70% yield of aldehyde from alcohol.

The oxidising mixture for this preparation is made by adding 115 c.c. of nitric acid (*d*, 1·42) to a mixture of 60 g. of sodium dichromate, 220 c.c. of water, and 20 g. of concentrated sulphuric acid (Wertheim, *J. Amer. Chem. Soc.*, 1922, **44**, 2658).

Oxidation of the higher alcohols with dichromate and not too dilute sulphuric acid yields appreciable amounts of esters with a number of other products such as aldehydes, acids and acetals. By choosing the appropriate conditions, good yields of the esters are often obtained (Franchimont and Zincke, *Annalen*, 1872, **163**, 197; Zincke, *ibid.*, 1869, **152**, 8; Pierre and Puchot, *ibid.*, 1872, **163**, 271; Bouveault, *Bull. Soc. chim.*, 1904, [iii], **31**, 1311; Reilly and Hickinbottom, *Proc. Roy. Dub. Soc.*, 1921, **16**, 246).

The formation of aldehydes and ketones from primary and secondary alcohols can be effected quite smoothly by catalytic dehydrogenation, and this process is admirably suited to their preparation in quantity. The most general method consists in passing the vapour of the alcohol over copper maintained at about 250—300° (Sabatier and Senderens, *Compt. rend.*, 1903, **136**, 738, 921, 983; E. F. Armstrong and Hilditch, *Proc. Roy. Soc.*, 1920, [A], **97**, 259; Weizmann and Garrard, *J.*, 1920, **117**, 324; see also Sabatier, *Catalysis in Organic Chemistry*, trsld. by Reid, 1923, pp. 650 *et seq.*).

The dehydrogenation follows the course

$$>\mathrm{CH(OH)}\cdot \qquad >\mathrm{C{:}O} + \mathrm{H_2},$$

and is reversible. If the reaction is used for the preparation of aldehydes in quantity it is better to arrange the process so that the unchanged alcohol is removed continuously from the product and returned to the system for further treatment. A type of apparatus which allows of this has been described by Bouveault (*Bull. Soc. chim.*, 1908, [iv], **3**, 120; compare Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, **7**, 90). A similar arrangement can be used for the preparation of ketones.

The catalyst is prepared by reducing cupric hydroxide, suspended in rolls of copper gauze and heated at about 300°, with hydrogen. The use of other supports for the cupric hydroxide is not recommended, as they may cause dehydration of the alcohol in a greater or less degree.

The method has been used successfully for the dehydrogenation of the lower primary and secondary monohydric alcohols, *cyclo*hexanol and some of its homologues, a few keto-alcohols, and also for the conversion of the ester of β-hydroxy*iso*hexane carboxylic acid to the corresponding keto ester. It is, however, not a satisfactory method for dehydrogenating unsaturated alcohols. These are generally converted, in great measure, into the corresponding saturated aldehydes or ketones. For alcohols of high molecular weight such as phenylethyl, decyl, or geraniol, it is necessary to carry out the dehydrogenation under reduced pressure, the apparatus described by Ruzicka (*loc. cit.*) being suitable for this purpose.

Other catalysts, as nickel, zinc, cadmium, or platinum, have also been used, but generally the reaction does not proceed so smoothly as with copper and gives undesirable by-products (compare Simington and Adkins, *J. Amer. Chem. Soc.*, 1928, **50**, 1449). Good results, however, appear to be obtained by the use of finely-divided silver, copper–silver, copper–zinc alloys or zinc oxide as catalysts (Moureu and Mignonac, *Compt. rend.*, 1920, **170**, 258; Ottensooser, *Bull. Soc. chim.*, 1927, [iv], **41**, 324).

A method has been described which appears to be useful for alcohols which are volatile only with difficulty (Rosenmund and Zetsche, *Ber.*, 1921, **54**, 1092, 2033). It consists in passing a current of air through a solution of the alcohol in cumene containing quinoline and *m*-dinitrobenzene and having metallic copper suspended in it. There are considerable differences in the optimal temperature for each alcohol, and the original papers should be consulted for details.

The direct oxidation of the monohydric primary alcohols to the corresponding acids generally succeeds best by the action of alkaline permanganate (see Fournier, *Bull. Soc. chim.*, 1909, [iv], **5**, 920). Less rarely chromic acid and sulphuric acid are used, for the product may contain esters, aldehydes, and acetals as by-products (see p. 87).

Preparation of iso*Butyric Acid from* iso*Butyl Alcohol.*—A solution of 280 g. of potassium permanganate in 5½ l. of water is added during a period of 3—4 minutes to a mixture of 100 g. of *iso*butyl alcohol and 300 c.c. of water containing 30 g. of sodium carbonate. The mixture is mechanically stirred and cooled to 4° by immersion in a bath of ice-water. The oxidation mixture is gradually allowed to attain room temperature. After about 12 hours the manganese dioxide is collected and the filtrate evaporated on the water-bath to about 300 c.c. It is then cooled, covered by a layer of ether, and acidified with dilute sulphuric acid. The aqueous layer, after the separation of the ether, is extracted 2 or 3 times with further amounts of ether. The combined ethereal extracts are fractionated after drying over sodium sulphate. The yield of acid is about 84% of theory.

This process of oxidation has been successfully applied to the preparation of *n*- and *iso*-valeric, *n*-hexoic, *n*-heptoic, and œnanthylic acids from the corresponding alcohols (Fournier, *loc. cit.*).

A special method for the oxidation of the monohydric aliphatic alcohols to the corresponding acids consists in heating the alcohol with caustic soda or potash in an autoclave at about 250—270° (Dumas and Stas, *Annalen*, 1840, **35**, 132). Thus, ethyl, amyl, and ceryl alcohols heated with potash lime yield hydrogen and the salt of the acid. *iso*Butyric acid is obtained similarly (Nef, *Annalen*, 1901, **318**, 173; compare Brodie, *ibid.*, 1848, **67**, 202). Weizmann and Garrard (*J.*, 1920, **117**, 332), working with *n*-butyl alcohol, found that by heating with caustic soda at 275° in an autoclave the evolution of hydrogen ceased after about 3 hours and good yields of *n*-butyric acid were obtained together with a small proportion of α-ethylhexoic acid. They also found that if *n*-butyl alcohol is heated with 10% of its weight of sodium at 275° the product consists of about equal weights of 2-ethylhexyl alcohol and *n*-butyric acid and a small amount of α-ethylhexoic acid. With higher proportions of sodium the yield of acid is increased at the expense of the alcohol.

Guerbet (*Compt. rend.*, 1912, **154**, 222, 1487; **155**, 1157; 1917, **164**, 952; **165**, 559) finds that when secondary alcohols are heated with caustic potash, condensation is the principal reaction, accompanied by oxidation. Thus *cyclo*hexanol yields 2-*cyclo*hexyl*cyclo*hexanol; *iso*propyl alcohol furnishes methyl *iso*amyl carbinol.

(b) *Elimination of the Elements of Water from Alcohols.*—The monohydric alcohols lose the elements of water to yield ethers or olefins according to the schemes (*a*) and (*b*):

$$2{>}\mathrm{CH{\cdot}\overset{|}{\underset{|}{C}}(OH)} \longrightarrow ({>}\mathrm{CH{\cdot}\overset{|}{\underset{|}{C}}})_2\mathrm{O} \quad . \quad . \quad . \quad (a)$$

$${>}\mathrm{CH{\cdot}\overset{|}{\underset{|}{C}}(OH)} \longrightarrow {>}\mathrm{C{:}C}{<} + \mathrm{H_2O} \quad . \quad . \quad (b)$$

The relative ease with which each of these reactions occurs depends on the type of alcohol, on the dehydrating agent employed, and on the general experimental conditions. In general, tertiary alcohols show the greatest tendency towards the formation of olefins, the elimination of water being effected under comparatively mild conditions, compared with those employed for primary and secondary alcohols. On the other hand, some alcohols are unable to yield olefins by reason of their structure, and consequently the effect of dehydration results in the production of ethers. In other alcohols it is usually possible to arrange conditions so that either the olefin or ether is the principal product.

The general methods of preparing olefins from alcohols fall into two groups. (*a*) Those in which the vaporised alcohol is passed over a heated catalyst such as alumina, aluminium silicates, tungsten oxide, or thoria. (*b*) The liquid alcohol is heated with a suitable reagent. For dehydration of this type very many reagents have been used—sulphuric acid with or without the addition of metal sulphates, phosphoric acid, oxalic acid, iodine, and the salts of weak bases with mineral acids. Of these, sulphuric acid has been employed extensively for the preparation of ethylene. Even this, the most favourable example of the use of sulphuric acid, is not satisfactory, as the ethylene evolved contains ether and is contaminated by sulphur dioxide and carbon dioxide. The proportion of these undesirable products can be reduced by the addition of small amounts of copper sulphate or vanadium pentoxide, but in spite of many investigations to improve the process it is still not so satisfactory as the catalytic method, or even the process involving the action of hot phosphoric acid (Moser and Lindinger, *Monatsh.*, 1923, **44**, 142; Senderens, *Compt. rend.*, 1923, **176**, 813; *Ann. Chim.*, 1922, [ix], **18**, 117; *Compt. rend.*, 1910, **151**, 392; Wöhler, *Annalen*, 1850, **91**, 127). The sulphuric acid method may be used for the immediate homologues of ethyl alcohol, but proportion of the acid should be reduced in order to prevent charring (compare Adams, Marvel, and Kamm, *J. Amer. Chem. Soc.*, 1918, **40**, 1950).

A good method for the preparation of ethylene and its immediate homologues consists in running the requisite alcohol on syrupy phosphoric acid maintained at 200—220° (Newth, *J.*, 1901, **79**, 915). Other methods include heating the alcohol with potassium hydrogen sulphate or aluminium sulphate, or adding the alcohol to zinc chloride at about 200°. The formation of olefins has been successfully accomplished from a number of secondary and tertiary alcohols by heating with *p*-toluenesulphonic acid (Wuyts, *Bull. Soc. chim. Belg.*, 1912, **26**, 304).

Preparation of cyclo*Hexene.*—A mixture of equal weights of *cyclo*hexanol and powdered potassium bisulphate—which has been recently fused—is heated in a round-bottomed flask fitted with an efficient fractionating column. The rate of heating is regulated so that the thermometer at the top of the column shows a temperature of about 70°. A mixture of water and *cyclo*hexene passes over. The distillate is made slightly alkaline by the addition of caustic alkali, the *cyclo*hexene separated, and after drying over sodium sulphate, distilled over sodium (Brunel, *Bull. Soc. chim.*, 1905, [iii], **33**, 270).

Preparation of Octylene.—Capryl alcohol is added gradually from a dropping funnel to a distillation flask containing fused zinc chloride heated in an oil-bath to about 200°. The distillate consists of octylene and water with a little unchanged alcohol. The upper layer of the olefin is separated, dried, and distilled over sodium. The product boils at 124—126° and is probably a mixture of isomers (Noorduyn, *Rec. trav. chim.*, 1919, **38**, 345).

Preparation of Amylene.—A mixture of 1500 c.c. of *iso*amyl alcohol and 100 c.c. of concentrated sulphuric acid is heated in a 3-litre flask fitted with a reflux condenser canted at 20° from the vertical. The condenser jacket is maintained at 60—90° so that the more volatile products pass through. They are condensed by a second and downward condenser. After 8 hours, distillation is stopped and the upper layer of the distillate separated. It is washed with dilute sodium hydroxide, dried, and distilled up to 100°. The residue is reserved for further preparations. The distillate is dried by solid caustic soda and fractionated. *iso*Amylene is collected at 32—42°—yield about 250 c.c.

The residue remaining after heating with sulphuric acid contains unchanged amyl alcohol and diamyl ether, which may be recovered by steam distillation and subsequent fractionation (Adams, Kamm, and Marvel, *J. Amer. Chem. Soc.*, 1918, **40**, 1950).

Senderens (*Compt. rend.*, 1912, **154**, 778) finds that tertiary alcohols and some of the higher secondary alcohols can be smoothly dehydrated by slow distillation with about 4% of concentrated sulphuric acid.

An elegant method for the dehydration of tertiary, and some secondary alcohols has been described by H. Hibbert (*J. Amer. Chem. Soc.*, 1915, **37**, 1748). It consists in distilling the alcohol slowly with a small amount of iodine and is exemplified by the following.

Preparation of Trimethylethylene.—*tert.*-Amyl alcohol (60 g.) and 0·14 g. of iodine are heated on a steam-bath for 24 hours, the vapour being passed through an efficient fractionating column. The distillate is collected in a cooled receiver, and after washing, drying, and a further distillation, is pure *iso*amylene, b. p. 36—37°, yield 27 g.

Preparation of Mesityl Oxide from Diacetone Alcohol.—Diacetone alcohol (700 g.) is distilled steadily through a fractionating column after adding 0·1 g. of iodine. The distillate collected up to 80° consists principally of acetone;

between 80° and 126° mesityl oxide and water are collected, while pure dry mesityl oxide is obtained at 126—131°. The upper layer of the second fraction is separated, dried over calcium chloride, and fractionated, when a further amount of mesityl oxide is collected at 126—131°.

A somewhat similar method has been employed by Kyriakides (*J. Amer. Chem. Soc.*, 1914, **36**, 991) for the dehydration of pinacone to form βγ-dimethylbutadiene. The elimination of the elements of water is effected by heating with a small amount of concentrated hydrobromic acid, trichloroacetic acid, or aniline hydrobromide. The method has been applied successfully to other glycols for the preparation of dienes and also for that of trimethylethylene. It appears that pinacone can also be dehydrated by heating with a trace of 20% sulphuric acid at 130—140°. The same change can be effected by heating with some sulphates such as copper sulphate or the alums (Bayer and Co., D.R.-P. 246,660, 249,030, 250,086, 253,081).

For the dehydration of menthenols to menthadienes an aqueous solution of oxalic acid has been used successfully (W. H. Perkin, jun., and Wallach, *J.*, 1910, **97**, 1436; Perkin, *ibid.*, p. 2142; Luff and Perkin, *ibid.*, p. 2154).

Catalytic methods yield themselves very conveniently to the preparation of olefins from primary and secondary alcohols. The vaporised alcohol is passed over alumina heated at 400—550°; a number of other catalysts have been employed, particularly kaolin and silicates of aluminium, and aluminium sulphate. Other substances, such as metaphosphoric acid, aluminium phosphate, and chromium phosphate, have been used to a less extent.

Alumina appears to be of fairly general application, and is best prepared by adding an aqueous solution of ammonia to a solution of aluminium sulphate. The alumina paste thus produced is thoroughly washed by decantation, and after mixing with small lumps of pumice, is drained as completely as possible. It is then packed into a quartz or iron tube and dried at a temperature of about 300°. During this period, the alumina should not be subjected to too high a temperature, which would cause it to lose its activity. The heating may be effected in a gas furnace. It is, however, more convenient to wind a suitable resistance round the tube, which can be embedded in kieselguhr or some other heat-insulating material, while the temperature can be controlled by a suitable thermo-couple.

The preparation of the olefin is effected by passing the vaporised alcohol over the alumina heated at 350—500°. The most favourable temperature must be determined experimentally. The method of collecting the olefin is determined by its nature. In the case of ethylene and other gaseous olefins, water and unchanged alcohol are removed by condensation and the gas is collected in a gas holder. It can also be condensed by liquid air or carbon dioxide and ether. For olefins which are liquid at room temperatures, the water and alcohol may be removed by fractional condensation, or the mixture of olefin and alcohol may be fractionated after drying.

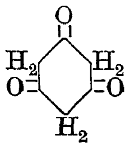
The elimination of the elements of water from butyl alcohol and most of the higher alcohols generally occurs to give a mixture of isomeric olefins (King, *J.*, 1919, **115**, 1404; Gillet, *Bull. Soc. chim. Belg.*, 1920, **29**, 192; 1921, **30**, 136, 226; Senderens, *Compt. rend.*, 1920, **171**, 916).

(3) *Special Reactions of Phenols.*

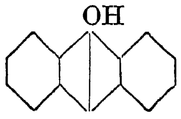
The hydroxy-derivatives of the aromatic hydrocarbons are distinguished from the alcohols by their more pronounced acid properties. While in general the monohydric phenols are only sparingly soluble in water, they dissolve readily in dilute aqueous solutions of the alkali hydroxides. They can be precipitated unchanged from such solutions either by the addition of acid or by saturating with carbon dioxide. It is evident that this reaction serves to distinguish between carboxylic acids, which liberate carbon dioxide from carbonates, and the phenols, which do not decompose carbonates. The presence of *nitro-*, or *halogen* groups in the nucleus enhances the acidic nature of the phenol, for many of them containing such groups decompose carbonate solutions, with the formation of phenates.

The di- and tri-hydroxy-derivatives of benzene and its homologues are solids of higher melting point, and are more soluble in water than the monohydric phenols. They lack the characteristic odour of the monohydric phenols and are further distinguished by their reducing properties. They reduce Fehling's solution and ammoniacal silver nitrate, while their alkaline solutions absorb oxygen from the air with the production of dark-coloured liquids. This aerial oxidation is more marked with phenols containing two hydroxyl groups in the *ortho* or *para* positions with respect to each other.

It is noteworthy that the *meta*-di- and tri-hydroxyphenols are capable of reacting in a tautomeric form. This is particularly so with phloroglucinol, which, in addition to its reactions as a phenol, yields a tri-oxime from the keto form (I). The γ-hydroxyanthracenes have been isolated in keto and enol forms, which are interconvertible. Thus γ-anthranol (II), an orange-coloured crystalline solid, readily soluble in dilute alkali, is converted by boiling in



(I.)



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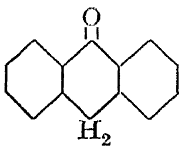

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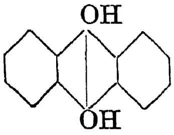

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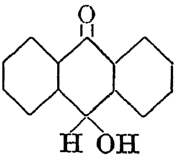


(V.)

glacial acetic acid into anthrone (III). This product has a much paler colour and is only soluble in alkali on warming, yielding a solution from which the original anthranol can be precipitated by the addition of excess of acid. An equilibrium mixture of the two forms is obtained by melting any one of them (K. H. Meyer, *Annalen*, 1911, **379**, 37; compare K. H. Meyer and Sander, *ibid.*, 1920, **420**, 113). Anthrahydroquinone (IV) isomerises similarly to oxanthrone (V)

The general reactions of the phenolic hydroxyl group have already been discussed. The hydroxyl group has an important influence on the reactivity of the aromatic nucleus and, in consequence, substitution in the nucleus takes place more readily than with the aromatic hydrocarbons. Not only do phenols more readily yield nitro- and halogen-substituted derivatives, but they can react with nitrous acid to give nitrosophenols, and with diazo-compounds to form hydroxy azo-compounds. Further, the carboxyl, aldehyde, and carbinol groups can be introduced into the nucleus by reactions which are not applicable to the hydrocarbons.

(a) *Formation of Nitroso-Derivatives.*—Nitrous acid reacts with phenols in aqueous or alcoholic solution to give nitrosophenols. In the benzene series the nitroso-group enters the *para* position with respect to the hydroxyl group. The methods of preparing nitrosophenols are illustrated by the following examples.

Preparation of p-*Nitrosophenol.*—A mixture of 150 g. of sulphuric acid and 400 c.c. of water is run slowly into a stirred solution of 60 g. of phenol, 54 g. of sodium nitrite, and 27 g. of sodium hydroxide in 150 c.c. of water cooled by an external bath of ice. After 2 hours, the *p*-nitrosophenol is collected and washed with ice-water. It is obtained in almost colourless needles by crystallisation from water (Bridge, *Annalen*, 1893, **277**, 85).

Preparation of Nitrosocarvacrol.—10 G. of carvacrol are dissolved in 40 c.c. of alcohol saturated at 0° by hydrogen chloride. A concentrated solution of 5 g. of sodium nitrite in water is added to the carvacrol solution cooled in ice. After some minutes the nitroso-compound separates as a thick paste. It is collected, washed with water, and crystallised from alcohol—yellowish needles, m. p. 153°.

Nitrosothymol is prepared similarly (Klages, *Ber.*, 1899, **32**, 1518).

Preparation of α-Nitroso-β-naphthol.—50 G. of β-naphthol are dissolved in a warm solution of 14 g. of sodium hydroxide in 600 c.c. of water contained in a 1500-c.c. beaker. The solution is cooled to 0° by a freezing mixture, and while it is stirred mechanically, 25 g. of powdered sodium nitrite are added.

Diluted sulphuric acid (110 g. *d* 1·32) is now added at such a rate that the temperature is maintained at 0°, crushed ice being added at intervals to check the rise in temperature. α-Nitroso-β-naphthol gradually separates during the reaction. The stirring is continued for about ½ hour after all the acid has been added. The product is then filtered off and washed with water. It is dried, at first in air and then in a vacuum desiccator—yield about 60 g., m. p. 106° (Marvel and Potter, *Organic Syntheses*, 1922, **2**, 61).

The nitrosophenols are tautomeric with the quinone monoximes, for the same product is obtained by the action of hydroxylamine hydrochloride on the appropriate quinone. Whether these compounds are to be represented by the phenolic formula or as derivatives of quinones, is not clear from the evidence of their reactions (see R. C. Farmer and Hantzsch, *Ber.*, 1899, **32**, 3101; Henrich, *J. pr. Chem.*, 1904, [ii], **70**, 313).

(b) *Formation of Nitro-Derivatives.*—The nitration of the phenols takes place readily; diluted nitric acid gives mononitro-compounds: more concentrated acid resulting in the formation of di- and tri-nitro-derivatives.

Preparation of o-*Nitro*-p-*Cresol.*—Diluted nitric acid (1 vol. conc. acid : 1 vol. water, 300 g.) is added to a mechanically stirred solution of 100 g. of *p*-cresol in 200 g. of benzene. The mixture is maintained at 20° during the nitration and the stirring continued for some hours after the addition of all the acid. When the nitration is complete, the two layers are allowed to separate and the lower layer of acid is removed. After washing the benzene solution with water, the solvent is driven over by a current of steam. As some of the nitrocresol passes over with the benzene, the distillate is made alkaline with caustic soda, and the benzene thoroughly washed with alkali. The alkaline solution thus obtained is acidified and added to the residue of crude nitrocresol, and the whole steam distilled. Pure *o*-nitro-*p*-cresol passes over—yield 126 g. yellow needles, m. p. 33° (G. Schultz, *Ber.*, 1907, **40**, 4324).

Nitration of m-*Cresol to give Mononitrocresols.*—A solution of 140 g. of *m*-cresol in 140 g. of glacial acetic acid cooled to − 5° is slowly poured into 200 g. of nitric acid (*d*, 1·5) diluted with 400 g. of glacial acetic acid and cooled to − 15°. The addition takes about 1½ hours, and the temperature must be kept below −1°. The nitration mixture is then poured on 1½ kg. of ice, and 1 kg. of water added. A reddish fluid mass separates, which, after keeping for 12 hours, solidifies. The solid is collected and washed with water. The filtrate and washings are extracted with ether and the combined extracts and solid are distilled in steam. By this means a separation is effected into volatile and non-volatile nitrocresols which are present in about equal amounts. The distillate deposits 4-nitro-*m*-cresol, m. p. 56° on cooling. From the aqueous portion of the distillate after the removal of the 4-nitrocresol, the isomeric 2-nitro-*m*-cresol can be obtained in small amount by extraction with ether. There remains in the distillation flask, 6-nitro-*m*-cresol, which is purified through its sodium salt. The free 6-nitrocresol separates from warm water in white needles, m. p. 129° (Khotinski and Jacopson-Jacopmann, *Ber.*, 1909, **42**, 3097; Staedel, *Annalen*, 1883, **217**, 51; Staedel and Kolb, *ibid.*, 1890, **259**, 210).

Preparation of 2 : 4 : 6-*Trinitroresorcinol* (*Styphnic Acid*).—Finely-powdered resorcinol is added—small portions at a time—to 5 or 6 parts of concentrated sulphuric acid warmed to 40°. The acid is stirred vigorously and the addition of resorcinol is discontinued till the previously added portion has dissolved. The heat evolved by the solution of the resorcinol is sufficient to maintain the mixture at 40° without any external heating. When all the resorcinol has been added, the solution is heated on a steam-bath till it solidifies to a stiff paste of small needles.

The mass is then cooled to 0°, and concentrated nitric acid—diluted with 10% of its weight of water—added, care being taken that the temperature does not rise above 2°. The reaction mass becomes yellow, and more and more crystalline material is deposited. Later, concentrated nitric acid and then fuming acid is added till about 2—2½ times the theoretical amount has been added. The reaction mixture is kept over-night and then poured gradually into 1½—2 volumes of water. The nitro-compound separates and is washed by decantation and then collected, m. p. 175° (Merz and Zetter, *Ber.*, 1879, **12**, 2037).

Orcinol can be nitrated similarly.

Preparation of Trinitrothymol.—A cold solution of 0·1 g. of thymol in 1 c.c. of cold concentrated sulphuric acid is added to a stirred mixture of 1 c.c. of concentrated nitric acid and 1 c.c. of concentrated sulphuric acid.

After warming for 3 or 4 minutes, it is poured into 20 c.c. of water, cooled, and stirred. The trinitro-compound which separates is collected, washed in water, and crystallised from water containing a little hydrochloric acid, m. p. 109—110° (Mulliken, *Identification of Pure Organic Compounds*, **1**, 110).

(c) *Formation of Halogen Derivatives.*—By the regulated action of chlorine or bromine on phenols, either alone or diluted by an anhydrous solvent such as glacial acetic acid, carbon tetrachloride, or chloroform, mono-, di-, or tri-substituted phenols are obtained. The halogens enter the *ortho* and *para* positions with respect to the hydroxyl. In the homologues of phenol, a similar orientation of the halogen is observed owing to the superior directing power of the hydroxyl group.

Prolonged action of the halogen, more particularly in presence of a catalyst, results in the formation of polyhalogen-substituted phenols. Thus, the chlorination of phenol at 70—75° in presence of a halogen carrier such as 2—3% of iodine or ferric chloride, yields 2 : 3 : 4 : 6-tetrachlorophenol, while *p*-cresol brominated in presence of aluminium furnishes 2 : 3 : 5 : 6-tetrabromo-*p*-cresol.

Preparation of 3-*Bromo*-p-*cresol.*—The calculated amount of bromine is added to *p*-cresol dissolved in 5 or 6 times its weight of chloroform. After keeping for 2 or 3 days, the solvent is evaporated and the residue distilled. 3-Bromo-*p*-cresol passes over at 218—219°.

3 : 5-Dibromo-*p*-cresol is prepared similarly by the action of the requisite amount of bromine on a solution of the cresol in chloroform. It is obtained as a crystalline solid, m. p. 49° from light petroleum.

The preparation of tribromo-*p*-cresol requires the presence of iron powder as a halogen carrier. The bromination is allowed to continue at room temperature for 2 or 3 days, when the solution is filtered and the solvent evaporated. The product is purified by crystallisation from dilute acetic acid, m. p. 102° (Zincke and Wiederhold, *Annalen*, 1902, **320**, 202).

Preparation of 6-*Chlorothymol.*—The calculated amount of chlorine—from a known weight of permanganate and an excess of hydrochloric acid—is passed into a solution of thymol in glacial acetic acid. The chlorothymol is precipitated by water and purified by recrystallisation from light petroleum, m. p. 58° (P. W. Robertson and Briscoe, *J.*, 1912, **101**, 1968).

Preparation of p-*Bromophenol.*—Phenol dissolved in its own volume of carbon disulphide is cooled in a freezing mixture of ice and salt and stirred mechanically. The calculated amount of bromine for the introduction of one bromo-group into the nucleus, diluted with its own volume of carbon disulphide, is then added from a tap funnel. The hydrogen bromide evolved during the reaction may be absorbed in water. When the reaction is complete, the solvent is removed by distillation from a boiling water-bath, and the residue distilled under reduced pressure. *p*-Bromophenol is collected at 145—150° at 25—30 mm. The first fractions contain some *o*-bromophenol and are collected separately.

For the distillation under reduced pressure Adams and Marvel (*Organic Syntheses*, 1921, **1**, 39) recommend the use of a Claisen flask in which the side arm outlet tube extends for a short distance into the neck of the flask. This prevents any vapour which has been in contact with the rubber bung being subsequently condensed to a discoloured liquid and running down the side arm into the receiver.

The chief fraction, by chilling and centrifuging, yields pure *p*-bromophenol (Adams and Marvel, *loc. cit.*).

In aqueous solution or suspension, bromination takes place readily, phenol yielding 2 : 4 : 6-tribromophenol by the action of bromine water. Excess of bromine water results in the formation of 2 : 4 : 6 : 6-tetrabromo*cyclo*hexadienone—" phenol tetrabromide " —which, however, by reaction with unchanged phenol is reconverted into tribromophenol. The *o*-, *m*-, and *p*-cresols yield similar types of compounds.

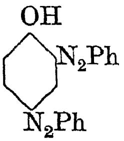
(d) *Reaction with Diazo-compounds.*—Phenols react with diazo-compounds in aqueous solution in the absence of free mineral acid to furnish highly-coloured hydroxyazo-compounds, the azo-group occupying the *ortho* or *para* position with respect to the hydroxyl.

$$Ph{\cdot}N_2{\cdot}Cl + C_6H_5{\cdot}OH \longrightarrow Ph{\cdot}N_2{\cdot}C_6H_4{\cdot}OH + HCl$$

The formation of such hydroxyazo-compounds is generally brought about by adding the aqueous diazo-solution to a solution of the phenol in dilute sodium hydroxide. If the phenol is soluble in water, sodium carbonate may be employed to neutralise the free acid of the diazo-solution and the acid liberated in the reaction. Hydroxyazo-compounds are also formed by adding aqueous solutions of the diazo-compound to the phenol in acetic acid in presence of sodium acetate.

This reaction is an important one, as it is employed not only for the recognition of diazo-compounds and of substances yielding diazo-compounds, but also for the industrial preparation of azo dyestuffs.

Coupling with diazo-compounds is not restricted to the introduction of one azo grouping. By increasing the concentration of the reactants there is a tendency to the formation bisazo-compounds, if the necessary positions in the nucleus are vacant. Thus phenol can yield the bisazo compound (VI) under suitable conditions. The introduction of a second azo grouping appears to be favoured by the presence of alkyl groups in the nucleus, particularly if they are in the *meta* position with respect to the hydroxyl. *m*-Dihydric phenols exhibit a similar tendency, yielding bis- and even tris-azo-compounds comparatively easily. Thus the monoazo-derivatives of resorcinol can be converted into (VII) and (VIII) and (IX).



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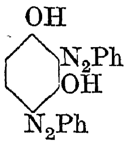

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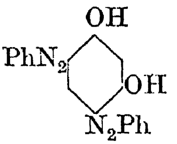

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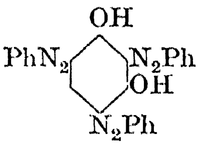
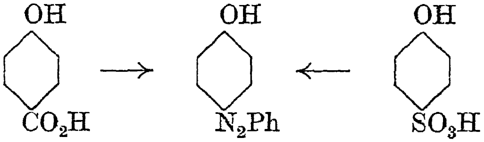


(IX.)

The homologues of phenol with alkyl groups in the *para* position, couple *ortho* to the hydroxyl. If a carboxyl or a sulphonic group is *para* to the hydroxyl, the coupling may take place with the expulsion of the group in the *para* position. Thus *p*-hydroxybenzoic acid couples with benzenediazonium salts to yield *p*-hydroxyazobenzene

(X); phenol-*p*-sulphonic acid behaves similarly, while resorcylic acid (XI) yields a mixture of (XII) and (XIII).



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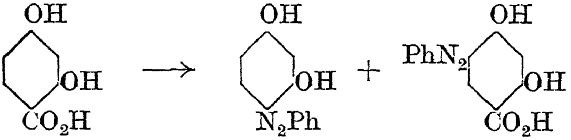


(XI.) (XII.) (XIII.)

The phenyl ethers are also able to couple, although not so readily as the phenols themselves. The coupling is effected in acetic acid solution, and usually requires a reactive diazonium salt such as those derived from *p*-nitraniline or 2 : 4-dinitraniline. Some phenol ethers undergo fission during coupling. Thus α-naphthyl phenyl ether or ethyl α-naphthyl ether yields a mixture of the azo-α-naphthyl ether and azo-α-naphthol (K. H. Meyer and Lenhardt, *Annalen,* 1913, **398**, 67; K. H. Meyer, Irschick, and Schlösser, *Ber.*, 1914, **47**, 1741).

(e) *Introduction of Aldehyde and Keto Groups.*—Phenols react with hydrogen cyanide and hydrogen chloride to give aldimines according to the scheme :

$$C_6H_5{\cdot}OH + HCN + 2HCl \longrightarrow HO{\cdot}C_6H_4{\cdot}CH{:}NH,HCl \xrightarrow{H_2O} HO{\cdot}C_6H_4{\cdot}CHO + NH_4Cl$$

Hydrolysis of the aldimine hydrochloride by water readily yields the aldehyde. This reaction is employed widely for the preparation of phenolic aldehydes. In applying it to the monohydroxy-derivatives of benzene and its homologues, it is necessary to carry out the reaction with hydrogen cyanide in presence of aluminium chloride using benzene as a solvent. Phenol ethers also react similarly under these conditions. The aldimine group enters the *para* position with respect to the hydroxyl group, unless this is already occupied, in which case an *o*-hydroxyaldehyde results after hydrolysis. The reaction proceeds more readily, however, if the *para* position is free. Dihydric phenols with the hydroxyl groups *meta* to each other yield aldimines particularly easily, the reaction being generally brought about in ethereal solution using zinc chloride as a condensing agent. These conditions can be applied successfully also to the mono- and the di-hydroxynaphthalenes. Phloroglucinaldehyde can be prepared particularly easily by this method, and it is even unnecessary to use a condensing agent. The following examples illustrate the different experimental modifications of this type of reaction (see Gattermann, *Annalen*, 1907, **357**, 313).

Preparation of p-*Hydroxybenzaldehyde.*—A mixture of 20 g. of phenol, 20 g. of anhydrous hydrogen cyanide, and 30 g. of benzene is cooled in a bath of ice and salt, and 30 g. of anhydrous and finely powdered aluminium chloride are gradually added. A lively evolution of hydrogen chloride occurs with the formation of aluminium phenolate. The mixture is now warmed under reflux at 40° and a moderate stream of hydrogen chloride passed in during 4 hours. The product is then poured carefully into ice-water acidified with hydrochloric acid, and from the mixture so obtained the benzene and most of the phenol are removed by distillation in steam. The aqueous solution remaining is saturated with salt and extracted with ether. After concentration of the ethereal extract, the hydroxyaldehyde is precipitated by the addition of sodium bisulphite, and subsequently liberated from the bisulphite compound, by treatment with dilute sulphuric acid. A greater part of the aldehyde is collected by filtration, and a further quantity can be obtained by extraction of the acid filtrate by ether—yield 30%, m. p. 116° (Gattermann, *Ber.*, 1898, **31**, 1766).

By a similar process, *o*-cresol gives a 35—40% yield of the corresponding aldehyde; *m*-cresol a 45—50% yield, while thymol gives an almost quantitative yield. It is noteworthy that the aldehyde from thymol does not form a bisulphite compound.

The aldehyde group can be introduced into the nucleus of phenol ethers by a similar method. The method has been applied successfully to anisole, phenetole, *m*-chloroanisole, *m*-chlorophenetole, diphenyl ether, veratrole, catechol diethyl ether, resorcinol dimethyl ether, α- and β-naphthyl ethers.

Preparation of 4-Hydroxynaphthaldehyde.—A mixture of 15 g. of α-naphthol, 15 g. of anhydrous zinc chloride, and 10 g. of hydrogen cyanide in 30 g. of dry ether is saturated with hydrogen chloride. After the stream of hydrogen chloride has been continued for about ½ hour a heavy oil commences to separate, which gradually increases in amount and eventually becomes crystalline. After about 2½ hours the reaction is complete, when the current of hydrogen chloride is discontinued. The ether is decanted from the solid matter, which, after washing with more ether, is heated with water. The aldehyde is obtained in almost quantitative yield, m. p. 181°.

β-Naphthol reacts similarly to give 2-hydroxynaphthaldehyde (Gattermann and v. Horlacher, *Ber.*, 1899, **32**, 284).

This method has also been applied to the preparation of aldehydes from pyrogallol, hydroxyhydroquinone, 1 : 5-dihydroxynaphthalene, 2 : 7-dihydroxynaphthalene, and 2 : 6-dihydroxynaphthalene.

Preparation of Resorcylaldehyde.—A solution of resorcinol (10 g.) in 30 g. of ether is mixed with 5 c.c. of anhydrous hydrogen cyanide in a small round-bottomed flask and a stream of hydrogen chloride passed in so that the excess escapes through the condenser. It is unnecessary to cool the reaction mixture. The aldimine hydrochloride separates out as a thick mass and partly as crystals on the side of the flask. After keeping for a few hours the ether is decanted off and the residue of aldimine hydrochloride washed with more ether. It is hydrolysed to the aldehyde by adding about 40 c.c. of boiling water. The hydrochloride dissolves completely and the aldehyde separates out on cooling in almost quantitative yield, m. p. 134°.

Orcin and xylorcin similarly react to give the aldehyde. Phloroglucinaldehyde is prepared similarly, except that it is necessary to hydrolyse the aldimine hydrochloride with dilute sulphuric acid (A. Robertson and Robinson, *J.*, 1927, 2202).

This reaction has been extended by its application to the synthesis of phenolic ketones by the condensation of *m*-di- and tri-hydric phenols with nitriles and hydrogen chloride (Hoesch, *Ber.*, 1915, **48**, 1122; Hoesch and v. Zarzecki, *ibid.*, 1917, **50**, 462). The reaction is quite similar in type to the Gattermann phenolaldehyde synthesis, and proceeds through the intermediate formation of an imine (H. Stephen, *J.*, 1920, **117**, 1529) according to the scheme

$$(HO)_2C_6H_4 + R{\cdot}CN + HCl \longrightarrow (HO)_2C_6H_3{\cdot}CR{:}NH,HCl \xrightarrow{H_2O} (HO)_2C_6H_3{\cdot}CO{\cdot}R + NH_4Cl.$$

The synthesis is illustrated by the following examples.

Preparation of Resacetophenone.—Powdered anhydrous zinc chloride (2 g.) is added to a solution of 5 g. of resorcinol and 3 g. of acetonitrile in 25 c.c. of dry ether. Dry hydrogen chloride is passed through the mixture. The zinc chloride gradually dissolves and the solution becomes warm. After about ½ hour a turbidity appears, and the solution subsequently sets to a thick paste. When the separation is complete, the flask is corked and set aside for several hours. Water (25 c.c.) is then added and the solution shaken with ether. The aqueous solution is heated for about ½ hour. On cooling an abundant separation of the hydroxy-ketone takes place. A further amount is obtained by ether extraction of the aqueous filtrate—yield 4·8 g., m. p. 144—145° after crystallisation from water. Orcin and resorcinol monomethyl ether react similarly. Benzonitrile, vanillic nitrile, and protocatechuic nitrile have been condensed with resorcinol and phloroglucinol to yield the corresponding hydroxy ketones (Hoesch, *loc. cit.*).

Preparation of Phloracetophenone.—A stream of dry hydrogen chloride is passed through a solution of 6 g. of phloroglucinol and 3 g. of acetonitrile. The separation of the ketimine commences after about ½ hour, and is complete after about 2 hours. The product is then kept for several hours, when it is taken up in water (100 c.c.). The aqueous solution is shaken with a further quantity of ether and about 20 c.c. of 5*N*-sulphuric acid are added. The ketimine sulphate separates as groups of thin colourless needles—yield 8·5 g.

The sulphate, heated with 15 times its weight of water for 15 minutes, is hydrolysed to phloroacetophenone, which separates on cooling in long, almost colourless needles (Hoesch, *loc. cit.*).

Karrer (*Helv. Chim. Acta*, 1919, **2**, 89) has prepared resorcyl- and phloroglucin-aldehydes by condensation of the appropriate phenol with cyanogen bromide in ethereal solution in presence of zinc chloride and hydrogen chloride.

A new method for the preparation of hydroxybenzophenones by the reaction of benzanilide imino-chloride, Ph·N:CCl·Ph, with resorcinol or phloroglucinol has been described by Stephen (*loc. cit.*).

A further method for the preparation of phenolic aldehydes has been described by Haakh (E.P. 157,850). It depends on the formation of an azomethine when a phenol is condensed with *p*-nitrosodiethylaniline in presence of formaldehyde.

The introduction of the aldehyde group into phenols can also be effected by reaction of the phenol in alkaline solution with chloroform (Reimer and Tiemann, *Ber.*, 1876, **9**, 824). The method has been found applicable, not only to homologues of phenol, but also to dihydric phenols and to some phenolic acids (Reimer and Tiemann, *Ber.*, 1876, **9**, 1271; Reimer, *ibid.*, 1878, **11**, 793; Tiemann and Schotten, *ibid.*, p. 773; Tiemann and Lewy, *ibid.*, 1877, **10**, 2211; Tiemann and W. H. M. Müller, *ibid.*, 1881, **14**, 1986; Tiemann and

Koppe, *ibid.*, p. 2015; Anselmino, *ibid.*, 1902, **35**, 4108; Chuit and Bolsing, *Bull. Soc. chim.*, 1906, [iii], **35**, 129; compare Auwers and Winternitz, *Ber.*, 1902, **35**, 465).

Preparation of Salicylaldehyde and p-*Hydroxybenzaldehyde*.—Phenol (30 g.) is dissolved in a solution of 60 g. of sodium hydroxide in 100 c.c. of water in a 1-l. flask fitted with a reflux condenser and a mechanical stirrer. The mixture is heated to 50—60° in a water-bath, and while it is stirred, chloroform (45 g.) is added gradually. When all the chloroform has been added, the mixture is boiled for ½ hour. It is then distilled to remove unchanged chloroform, then strongly acidified with hydrochloric acid and steam distilled.

Salicylaldehyde and unchanged phenol are driven over with the steam. They are removed from the distillate by ether and the aldehyde is removed from the ether solution by shaking with a saturated solution of sodium bisulphite. The crystalline bisulphite compound thus obtained is collected and washed with ether and finally with a little alcohol to remove phenol. By warming the purified bisulphite compound with dilute sulphuric acid, the aldehyde is liberated. It is separated with the aid of ether, the ethereal solution dried in contact with anhydrous sodium sulphate and distilled, b. p. 195°—yield about 6 g.

The aqueous solution remaining after the removal of salicylaldehyde from the original reaction product contains *p*-hydroxybenzaldehyde and suspended tarry matter. It is filtered while still hot through a damp filter-paper. The filtrate, after cooling, is extracted with ether. After drying the ethereal solution in contact with anhydrous sodium sulphate, the solvent is distilled off, leaving *p*-hydroxybenzaldehyde in an approximately pure condition. It may be further purified by crystallisation from hot water or through its bisulphite compound, which is readily soluble in water, m. p. 115°—yield about 1 g. (Reimer and Tiemann, *Ber.*, 1876, **9**, 824; Tiemann and Herzfeld, *ibid.*, 1877, **10**, 63, 213).

Preparation of β-Hydroxy-α-naphthaldehyde.—Chloroform (400 g.) is added drop by drop to a solution of 400 g. of β-naphthol in a mixture of 1650 c.c. of water and 1200 g. of alcohol (90%) containing 800 g. of sodium hydroxide. The commencement of the reaction is recognised by development of a blue coloration. During the course of the reaction heating should be stopped, as the heat liberated is sufficient to continue the condensation. The addition of the chloroform generally requires about an hour, and the end of the reaction is recognised by the colour of the reaction mixture changing to a light red, which neither the addition of more alkali nor more chloroform can change.

The alcohol is then distilled off and the residue acidified with hydrochloric acid. The crude hydroxyaldehyde separates as an oil, which is removed with ether, dried in contact with anhydrous sodium sulphate, and distilled under reduced pressure, b. p. 192°/27 m.m.—yield 86% of theory (Fosse, *Bull. Soc. chim.*, 1901, [iii], **25**, 373).

(f) *Introduction of Carboxyl Group*.—It was found by Kolbe (*J. pr. Chem.*, 1874, [ii], **10**, 94) that sodium phenate yields a salt of salicylic acid by heating in a stream of carbon dioxide. This reaction apparently depends on the formation of sodium phenyl carbonate, which is converted into sodium salicylate by intramolecular rearrangement (R. Schmitt, *J. pr. Chem.*, 1885, [ii], **31**, 397); Tijmstra considers, however, that the reaction is primarily dependent on the direct interaction of carbon dioxide with the aromatic nucleus (*Ber.*, 1904, **38**, 1375; compare Tijmstra and Eggink, *ibid.*, 1906, **39**, 14; Tijmstra, *ibid.*, 1912, **45**, 2837).

The reaction is brought about most effectively either by heating sodium phenyl carbonate in an autoclave at 130°, or simply by passing carbon dioxide into dry sodium phenate heated under pressure at 130—140° till there is no further absorption of the carbon dioxide. The temperature and the nature of the alkali salt appear to have an influence, for sodium phenate treated with carbon dioxide under pressure at temperature above 140° furnishes some *p*-hydroxybenzoic acid. This acid is produced in good yield by the action of carbon dioxide on potassium phenate at 180°. The alkali salts of the homologues of phenol show a similar behaviour to carbon dioxide. The reaction of carbon dioxide with the alkali salts of β-naphthol is very interesting, for by suitably altering the conditions, the carboxyl group may be introduced into positions 1-, 3-, or 6- (compare Morgan, *J. Soc. Chem. Ind.*, 1931, **50**, 104).

In the case of the di- and tri-hydric phenols the introduction of the carboxyl group can be brought about by milder conditions—namely, by heating with fairly concentrated aqueous solutions of alkali bicarbonates at about 130°. If the hydroxyls are in the *meta* position, as in resorcinol or phloroglucinol, the reaction goes particularly easily, and can be effected by heating for a short time in an open flask with bicarbonate solution, preferably in a stream of carbon dioxide (Will and Albrecht, *Ber.*, 1884, **17**, 2103; Bistrzycki and v. Kostanecki, *ibid.*, p. 1985; v. Kostanecki, *ibid.*, p. 3202; Thiele and Jaeger, *ibid.*, 1901, **34**, 2840).

Preparation of Resorcylic Acid.—Resorcinol (20 g.) is heated in a flask with 100 g. of potassium bicarbonate and 200 c.c. of water for about 1½ hours and the solution finally boiled vigorously. It is then cooled, acidified with hydrochloric acid, and extracted with ether. The resorcylic acid is removed from the ether extract by shaking it with aqueous bicarbonate solution, acidifying the latter solution, and extracting with ether. Evaporation of this last ether extract yields crude resorcylic acid, which after crystallisation from water is obtained pure. The acid separates in hydrated crystals. The anhydrous acid has m. p. 213° (with rapid heating).

Orcinol hehaves similarly.

K. Brunner (*Annalen*, 1907, **351**, 319) describes conditions for the introduction of the carboxyl group which consists in heating the di- or tri-hydric phenol in glycerol solution with bicarbonate in a stream of carbon dioxide at temperatures between 130° and 210°. By this process the temperature at which the reaction is effected may determine the nature of the product. Thus resorcinol at 180° gives β-resorcylic acid in almost quantitative yield, while at 130° the yield of acid is only 40%, and the product consists almost entirely of γ-resorcylic acid. The use of higher temperatures may result in the formation of dibasic acids.

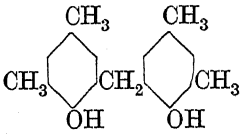
Another method for the preparation of phenolcarboxylic acids is the reaction of the phenol with carbon tetrachloride in alkaline solution (Reimer and Tiemann, *Ber.*, 1876, **9**, 1285; Hasse, *ibid.*, 1877, **10**, 2185). It is analogous in principle to the preparation of the hydroxyaldehydes from phenols and chloroform. The principal product is the *p*-hydroxy-acid, if the *para* position is free. This reaction has been applied to the introduction of a carboxyl group into nitro- and chloro-phenols.

(g) *Lederer–Manasse Reaction.*—Phenols can condense with aqueous formaldehyde in alkaline solution with the formation of hydroxybenzyl alcohols, the $-CH_2\cdot OH$ group entering the *ortho* and *para* positions (Lederer, *J. pr. Chem.*, 1894, [ii], **50**, 223; Manasse, *Ber.*, 1894, **27**, 2409; 1902, **35**, 3844).

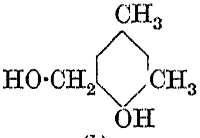
The general method of procedure consists in adding about 1 mol. prop. of formalin solution to a solution of 1 mol. prop. of the phenol in somewhat more than the necessary amount of dilute sodium hydroxide solution. The solution is kept till the odour of formalin has gone, when the alkali is neutralised by the addition of a moderate excess of dilute acid. The product is extracted with ether.

This simple condensation is frequently accompanied by the formation of smaller or greater amounts of diphenylmethane derivatives in which 2 mol. props. of phenol react with 1 mol. prop. of formaldehyde. The formation of these compounds appears to be dependent also on the reactivity of the phenol. This type of condensation is, however, favoured by vigorous condensing agents. Thus *m*-xylenol reacts with formaldehyde solution under the influence of dilute aqueous sodium hydroxide solution (1—2% solution) to give (*a*). If slaked lime is used as condensing agent the normal product (*b*) is obtained (Manasse, *Ber.*, 1902, **35**, 3844; v. Auwers, *ibid.*, 1907, **40**, 2526). β-Naphthol behaves similarly.

A number of condensing agents other than alkali have been used—barium hydroxide, sodium carbonate, zinc oxide, potassium carbonate. Generally, examples of the use of these substances are confined to the patent literature.



(*a*)

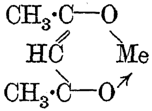


(*b*)

(4) *Enolic Compounds.*

The grouping $>C\!:\!\dot{C}\cdot OH$ present in phenols is also characteristic of the enolic forms of ketones, and consequently enolic compounds resemble the phenols in many of their reactions. Thus, the enolic forms of 1 : 3-di-ketones and β-ketonic esters give colorations with ferric chloride and are acidic in character, dissolving in aqueous alkali to give alkali salts. Other metal salts are known, the copper salts in particular being employed for the isolation of the pure diketones from mixtures, as well as for their characterisation. The metal derivatives of acetyl acetone are best known, more than sixty having been prepared (Combes, *Compt. rend.*, 1887, **105**, 868; Tanatar and Kurovski, *J. Russ. Phys. Chem. Soc.*, 1906, **40**, 580; Kurovski, *Ber.*, 1910, **63**, 1078; Morgan and H. W. Moss, *J.*, 1914, **105**, 189; Morgan and H. D. K. Drew, *ibid.*, 1924, **125**, 372, 1264;

Morgan and Bowen, *ibid.*, p. 1252). Most of these compounds are not normal salts, in that many of them are soluble in hydrocarbons, sparingly soluble in water, and can be volatilised without decomposition. They are to be considered as co-ordination compounds, in which the carbonyl group is attached to the metal by a co-ordinate link according to the formula



The reaction of the alkali derivatives of the enols with alkyl halides and acyl halides is very interesting. In general, the alkyl halides do not yield the corresponding ethers as the principal product, but a ketone in which the alkyl group is attached to the α-carbon atom. Thus the sodium derivative of acetoacetic ester (I) gives with methyl iodide, α-methylacetoacetic ester (II)

$$\underset{\text{(I.)}}{CH_3{\cdot}C(ONa){:}CH{\cdot}CO_2Et} + CH_3I \longrightarrow \underset{\text{(II.)}}{CH_3{\cdot}CO{\cdot}CH(CH_3){\cdot}CO_2Et} + NaI$$

$$CH_3{\cdot}C(ONa){:}CH{\cdot}CO{\cdot}CH_3 + CH_3I \longrightarrow CH_3{\cdot}CO{\cdot}CH(CH_3){\cdot}CO{\cdot}CH_3 + NaI$$

The sodium derivative of acetyl acetone gives similarly $(CH_3{\cdot}CO)_2CH(CH_3)$. Compare the behaviour of resorcinol and phloroglucinol towards alkylation, and also the action of some halides on the sodium salts of phenols suspended in non-dissociating solvents (p. 74).

The reaction of the alkali salts of the enols with alkyl halides is one which has most important applications in synthetical work, and especially with β-keto esters such as acetoacetic ester.

Preparation of mono*Alkyl Derivatives of Acetoacetic Ester.*—To an alcoholic solution (about 10% concentration) of sodium ethoxide (1 mol.) is added the necessary amount of acetoacetic ester (1 mol.). A slight excess of the appropriate alkyl halide is then added and the mixture heated under reflux till it is no longer alkaline to moist litmus paper.

The greater part of the alcohol is distilled off, water added to the residue, and the oil taken up in ether. After washing the ethereal solution with water, it is dried over anhydrous sodium sulphate, then evaporated, and the residue fractionated under reduced pressure (W. Wislicenus, *Annalen*, 1877, **186**, 216; Conrad and Limpach, *ibid.*, 1878, **192**, 153).

The introduction of a second alkyl group can be effected in the same way. It is usually unnecessary to isolate the monoalkyl compound, for the neutral alcoholic solution resulting after the reaction of 1 mol. prop. of alkyl halide can be treated with a further equivalent of alcoholic ethylate and alkyl halide. The subsequent operations are similar to those described above.

Michael and Wolgast (*Ber.*, 1909, **42**, 3176) consider that the usual method of purifying the monoethyl derivative of acetoacetic ester is not sufficient to remove all the diethyl derivative. The following is a description of the purification of the crude product of the reaction between ethyl iodide and sodium acetoacetic ester and its subsequent hydrolysis to methyl propyl ketone.

The crude product is shaken with dilute aqueous ammonia to remove acetoacetic ester. The oil is separated and fractionated. The distillate, collected over approximately the right range, is shaken for 15 minutes at room temperature with an excess of 5% aqueous potassium hydroxide. Hydrolysis of the monoethyl derivative occurs rapidly under these conditions, while the diethyl derivative is scarcely attacked. The oil is then separated, while the aqueous alkaline solution is kept for 24 hours. It is then acidified with dilute hydrochloric acid and gradually heated under reflux. The evolution of carbon dioxide takes place at about 40—50°, and after heating for about 6 hours the decomposition is complete. The ketone is then distilled off.

Preparation of 3-Methylpropionyl Acetone.—The sodium salt of propionyl acetone is prepared by adding the requisite amount of sodium to an ethereal solution of the diketone. The air-dried sodium salt is heated under an efficient reflux with 4 parts of methyl iodide at 110°, and after about 1 hour the temperature is raised to 140—150°. After cooling, the mixture is shaken with water. The organic liquid is removed by ether.

Fractionation of the dried ethereal solution yields 3-methylpropionyl acetone, b. p. 85—87°/11 mm. 3-Ethylpropionyl acetone, 3-butylacetyl acetone, 3-ethylbutyryl acetone, and dipropionylethylmethane have been prepared by a similar process (Morgan and Drew, *J.*, 1924, **125**, 745; Morgan and Thomason, *ibid.*, p. 757; Morgan and Holmes, *ibid.*, p. 760).

Preparation of 3 : 3-Dimethylacetyl Acetone.—61 G. of the sodium derivative of 3-methylacetyl acetone and 250 g. of methyl iodide are heated at 120—160° for 4 hours. The product is worked up as described above. Yield 23 g., b. p. 61—62°/9 mm. (Morgan and Drew, *J.*, 1924, **125**, 1601).

Although the O-ether is not produced by the alkylation of the sodium salts of enolic compounds, it is usually possible to obtain it in small amount by using the silver salt. Thus the silver salt of the enolic form of acetoacetic ester yields some of the O-ether, β-ethoxycrotonic ester (Nef, *Annalen*, 1893, **276**, 202; Lander, *J.*, 1903, **83**, 416). The silver salt of the enolic form of ethyl oxaloacetate gives, however, the ethyl ether $EtO_2C{\cdot}C(OEt){:}CH{\cdot}CO_2Et$ as the principal product. Morgan and Drew (*J.*, 1921, **119**, 614) have described a novel method of preparing the ether of the enolic form of acetyl acetone.

Acyl halides react with the sodium salts of enolic compounds to give, in most cases, the C-derivative. Thus the sodium derivative of acetoacetic ester reacts with acetyl chloride or benzoyl chloride to yield compounds of the type $CH_3{\cdot}CO{\cdot}CH(COR){\cdot}CO_2Et$.

Preparation of Benzoyl Acetoacetic Ester.—For every 100 g. of acetoacetic ester mixed with 300 c.c. of alcoholic solution containing 17·7 g. of dissolved sodium, and cooled to 5°, 45 c.c. of benzoyl chloride are added from a burette with stirring. After keeping for ½ hour, add a further 150 c.c. of ethoxide solution and 22·5 c.c. of benzoyl chloride. The addition of more benzoyl chloride and ethoxide solution is continued till 600 c.c. of ethoxide have been added, the amount of each reagent being half of the amount added previously. The solution is kept for 12 hours after all the chloride has been added, and is then filtered. The residue of sodium chloride and the sodium salt of benzoyl acetoacetic ester is washed with ether. The benzoyl derivative is isolated by treatment with water and acidification with acetic acid, followed by extraction with ether (Claisen, *Annalen*, 1896, **291**, 67; E. Fischer and Bülow, *Ber.*, 1885, **18**, 2131).

The reaction between the sodium salt and the acyl chloride is more usually effected in an indifferent solvent.

Preparation of Benzoyl Acetoacetic Ester.—Acetoacetic ester dissolved in 6—7 times its weight of ether is treated with 1 atomic proportion of sodium wire and kept till all the metal has been converted into the sodium salt. A solution of the requisite amount of benzoyl chloride in ether is then added. When the odour of the chloride has disappeared, the ether is washed with water and dried. Evaporation of the solvent yields the benzoyl derivative (James, *Annalen*, 1884, **226**, 220).

It is interesting to note that while the acyl halides, in general, substitute the methylene group, chloroformic ester, $Cl{\cdot}CO_2Et$, reacts with the sodium derivative of acetoacetic ester to give a high proportion of the true enolic derivative $CH_3{\cdot}C(O{\cdot}CO_3Et){:}CH{\cdot}CO_2Et$ (Nef, *Annalen*, 1891, **266**, 52).

The true acyl derivatives of the enolic forms of acetoacetic ester are most conveniently prepared by reaction of the ester with the appropriate acyl halide in pyridine solution.

Preparation of Acetoxycrotonic Ester.—Acetyl chloride ($1\frac{1}{2}$ mol. props.) is added to a solution of acetoacetic ester (1 mol. prop.) in 2 mol. props. of pyridine. The mixture must be cooled during the addition of the acyl halide. The solution soon sets to a paste of pyridine hydrochloride. After keeping it for 1 or 2 days, ether is added and the insoluble pyridine salt collected. The ethereal filtrate is shaken with dilute sodium hydroxide solution, then with dilute sulphuric acid, and finally with water. After drying, the solution is fractionated giving the acetyl derivative, b. p. 112—113°/17 mm. The yield is approximately equal to the weight of acetoacetic ester taken (Claisen and Haase, *Ber.*, 1900, **33**, 1242, 3780).

Reaction of enols with bromine takes place readily, and in alcoholic solution it is stated to take place instantaneously. The method has been used successfully for the estimation of the proportion of enol in mixtures containing the keto form, since the keto compound is not seriously attacked by bromine during the period of the estimation. The reaction probably takes place according to the following scheme giving α-bromo ketone :—

$$>C{:}\overset{|}{C}{\cdot}OH + Br_2 \longrightarrow >\overset{|}{C}Br{\cdot}\overset{|}{C}(OH)Br \longrightarrow >CBr{\cdot}C{:}O + HBr.$$

The estimation consists in adding to the keto-enol mixture a solution of bromine in alcohol from a burette till the colour is no longer discharged. If the concentration of the bromine solution is known accurately, the volume used provides a measure of the amount of enol in the mixture. As the concentration of the alcoholic solution of bromine changes rapidly, it is better to estimate the amount of bromo ketone by adding to the solution potassium iodide and concentrated hydrochloric acid. After warming, the liberated iodine is titrated with standard thiosulphate (K. H. Meyer, *Annalen*, 1911, **380**, 216).

Enols resemble the phenols also in their ability to react with diazo-solutions to give azo-compounds. The coupling is best effected by adding the aqueous solution of the diazo-compound to an alcoholic solution of the β-keto ester or 1 : 3-diketone, and then adding sodium acetate (C. Bülow, *Ber.*, 1899, **32**, 197; Morgan and Reilly, *J.*, 1913, **103**, 810; compare V. Meyer, *Ber.*, 1877, **10**, 2075; Züblin, *ibid.*, 1878, **11**, 1417; v. Richter and Münzer, *ibid.*, 1884, **17**, 1926; Beyer and Claisen, *ibid.*, 1888, **21**, 1697). It sometimes happens that, during coupling, groups are split off—for example, in the coupling of 3-methyl acetyl acetone to yield a derivative of methyl ethyl ketone (Morgan and Reilly, *loc. cit.*), or in the behaviour of malonic acid with diazo-compounds (v. Pechmann, *Ber.*, 1892, **25**, 3175; Busch and Wolbring, *J. pr. Chem.*, 1905, [ii], **71**, 370).

(5) *Mercaptans and Thiophenols.*

The sulphur analogues of the alcohols—the mercaptans—are neutral liquids of persistent and generally not pleasant odour. They show a more pronounced tendency than the alcohols towards the formation of metal derivatives. Solutions of the alkali salts are obtained by dissolving the mercaptan in aqueous alkali, while the dry alkali salt is prepared by reaction of the dry mercaptan, preferably diluted with an inert solvent, with the alkali metal. Of the other metal salts, those of lead and mercury are the most important, since many of them have definite melting points and are used to characterise the mercaptans.

Preparation of Lead and Mercury Salts of the Mercaptans.—A solution of the mercaptan (6 drops) in 2 c.c. of alcohol is treated with an excess of 20% lead acetate solution or of 10% mercuric cyanide. On cooling, the precipitated mercaptide is collected and dried on porous earthenware. The mercury salts are best purified by crystallisation from alcohol. This process is recommended by Wertheim for the characterisation of small amounts of mercaptans (*J. Amer. Chem. Soc.*, 1929, **51**, 3661).

This process can be used for the preparation on a larger scale, or the mercury salts may be obtained by the action of mercuric oxide on the mercaptan.

The mercaptans resemble the phenols in that they can be alkylated to thioethers in alkaline solution by alkyl halides, or by alkyl sulphates or alkyl esters or arylsulphonic acids. The thiophenols behave similarly.

Preparation of Thioethers.—A slight excess of dialkyl sulphate or alkyl ester of an arylsulphonic acid is added to a solution of the mercaptan or thiophenol in 15—20% of aqueous sodium hydroxide solution (20% excess of alkali). The mixture is then refluxed for 2—3 hours, when the oil which has separated is removed, dried over potassium carbonate, and distilled (compare Gilman and Beaber, *J. Amer. Chem. Soc.*, 1925, **47**, 1449).

The preparation of the 2 : 4-dinitrophenyl thioethers from mercaptans by reaction with 2 : 4-dinitrochlorobenzene has been recommended as a method for the characterisation of mercaptans. Bost, Turner, and Norton (*J. Amer. Chem. Soc.*, 1932, **54**, 1985) describe the following procedure

A solution of 0·01 g.-mol. of the mercaptan in 30 c.c. of absolute alcohol is mixed with the theoretical amount of sodium hydroxide in 3 c.c. of alcohol and 0·01 g.-mol. of 2 : 4-dinitrochlorobenzene in 10 c.c. of alcohol. The reaction is completed by heating in a water-bath for 10 minutes. The solution is filtered while still hot. The thioether crystallises out on cooling.

Oxidation of the thioether to the corresponding sulphone is recommended as a further characterisation (see p. 115).

There appears to be some tendency for the mercaptans to form esters by reaction with organic acids according to the scheme

$$C_6H_5{\cdot}CO_2H + EtSH \longrightarrow C_6H_5{\cdot}CO{\cdot}SEt + H_2O$$

The reaction is a reversible one, and the tendency to ester formation is much less than with the alcohols (compare Reid, *Amer. Chem. J.*, 1910, **43**, 489; J. H. Sachs and Reid, *ibid.*, 1916, **38**, 2746; Faber and Reid, *ibid.*, 1917, **39**, 1930; L. S. Pratt and Reid, *ibid.*, 1915, **37**, 1934.)

In their behaviour towards oxidation, the mercaptans and thiophenols differ markedly from the alcohols and phenols. The main products are disulphides of the type R·S·S·R or sulphonic acids. Either of these two types can be obtained by suitably regulating the conditions.

The formation of disulphides from the mercaptans has been brought about by a number of methods—the action of concentrated sulphuric acid, of sulphuryl chloride, of ferric chloride, or of bromine. The most convenient method is by the use of iodine due to Kekulé and Linnemann (*Annalen*, 1862, **123**, 277).

Preparation of Diethyl Disulphide.—Finely-powdered iodine, slightly less than the theoretical amount, is added gradually to a mechanically stirred solution of ethyl mercaptan in a slight excess of 15% sodium hydroxide solution. The separation of the disulphide commences immediately, and after the whole of the iodine has been added the almost colourless oil is taken up in ether, washed with dilute sodium hydroxide solution and water, dried, and fractionated. Diethyl disulphide is obtained as a colourless liquid of pleasant ethereal odour, b. p. 152—153° (Kekulé and Linneman, *loc. cit.*; compare Smythe, *J.*, 1909, **95**, 349).

For the oxidation of thiol-substituted acids to the corresponding disulphides ferric chloride has been successfully used (Claëssen, *Ber.*, 1883, **14**, 410).

The formation of disulphides from thiophenols proceeds very readily. An alcoholic solution of thiophenol containing aqueous ammonia deposits diphenyl disulphide on spontaneous evaporation. Homologues of diphenyl disulphide and some of its nitro- and hydroxy-substituted derivatives have been prepared similarly from the corresponding thiophenols (Leuckart, *J. pr. Chem.*, 1890, [ii], **41**, 179). Other methods of preparation include the oxidation of the thiophenol with ferricyanide (Leuckart, *loc. cit.*), dilute nitric acid (Otto, *Annalen*, 1867, **143**, 213), or ferric chloride.

*Preparation of Di-*p*-tolyl Disulphide.*—A solution of 12·5 g. of thio-*p*-cresol in 50 c.c. of acetic acid is heated for a short time with an excess of 40% ferric chloride solution (50 g.). The disulphide which separates is washed successively with hydrochloric acid and water, dried on a tile, and recrystallised (Zincke and Frohneberg, *Ber.*, 1910, **43**, 840).

The vigorous oxidation of mercaptans leads to the formation of sulphonic acids. Heating with concentrated nitric acid is the method usually employed for the alkyl mercaptans (Löwig and Weidmann, *Pogg. Annalen*, 1840, **49**, 329; Kopp, *Annalen*, 1840, **35**, 343; Noller and Gordon, *J. Amer. Chem. Soc.*, 1933, **55**, 1093). Autenrieth (*Annalen*, 1890, **259**, 363) claims that the oxidation of ethyl mercaptan by means of permanganate gives a better yield of the sulphonic acid. It should be noted, however, that benzyl mercaptan gives benzoic acid on oxidation.

In the aromatic series the use of nitric acid is often attended by the formation of other products. Zincke and Frohneberg (*Ber.*, 1910, **43**, 857) have described a simple method of converting the thiophenol into the corresponding sulphonyl chloride or bromide by the action of chlorine or bromine.

Preparation of p-*Toluenesulphonyl bromide from Thio*-p-*cresol.*—A solution of 3 g. of thio-*p*-cresol in 5 times its weight of acetic acid is treated gradually with 6 g. of bromine. When the reaction is complete, the solvent is evaporated, leaving the crystalline bromide stained by bromine. It is pressed on a tile and recrystallised from light petroleum, m. p. 93—94° (Zincke and Frohneberg, *loc. cit.*).

The alkyl mercaptans react with the carbonyl group of aldehydes and ketones to give compounds which are the thio analogues of the acetals, and which are designated mercaptals. They differ from the acetals in being scarcely attacked by acids. They are very stable compounds, alkalis having practically no action on them, while oxidation usually converts them into disulphones.

The condensation between the carbonyl compound and the mercaptan is generally effected by the action of zinc chloride or fuming hydrochloric acid on a mixture of the reactants. It can also be brought about by passing hydrogen chloride into the mixture (Baumann, *Ber.*, 1885, **18**, 884; 1886, **19**, 2803).

Thiol acids such as thioglycollic acid—$HS{\cdot}CH_2{\cdot}CO_2H$—or thiolactic acid—$CH_3{\cdot}CH(SH){\cdot}CO_2H$—react with aldehydes without the addition of any catalyst. Thus benzaldehyde mixed with 2 mol. props. of thioglycollic acid solidifies after a few minutes to give $Ph{\cdot}CH{:}(S{\cdot}CH_2{\cdot}CO_2H)_2$. A 40% solution of formaldehyde behaves similarly.

(6) *Ethers.*

In all ethers, two hydrocarbon residues or substituted radicles are joined together by an oxygen atom. They can be represented by the general formula $R{\cdot}O{\cdot}R'$, where R and R are alkyl or aryl groupings.

(a) *Fission of Ethers.*—The oxygen link is, in general, indifferent to alkalis, ammonia, or amines. Alkali metals also have no action, therefore the aliphatic ethers are very conveniently dried by distillation over metallic sodium. This stability is modified, however, by the presence of substituents—at least as far as the aryl ethers are concerned. This is discussed on p. 112.

The ethers are, however, more sensitive to acids. Thus acetals—which contain the grouping $>C(O{\cdot}Alk)_2$ and are dialkyl ethers of the ortho form of aldehydes and ketones—are hydrolysed by dilute aqueous acid to yield the corresponding carbonyl compound and the alcohol.

Dialkyl ethers are not appreciably altered by dilute aqueous mineral acids. Fission occurs on heating with concentrated acid, according to the following scheme, which represents the action of concentrated hydriodic acid, the most convenient reagent for the purpose :

$$R{\cdot}O{\cdot}R + HI \qquad RI + R{\cdot}OH$$

The lower aliphatic ethers dissolve in concentrated sulphuric acid with the evolution of heat and the formation of alkyl hydrogen sulphate, from which the alcohol may be obtained by diluting with water and distilling. By heating the solution of the ether in concentrated sulphuric acid or, better, by reaction of the ether with sulphur trioxide, the corresponding dialkyl sulphate is formed (P. Claesson, *J. pr. Chem.*, 1879, [ii], **19**, 257; compare Blackler, *Chem. News*, 1901, **83**, 303).

$$(C_2H_5)_2O + SO_3 \qquad Et_2SO_4$$

The aryl alkyl ethers are more stable towards acids, in that the action of concentrated sulphuric or nitric acids leads to substitution in the nucleus. Fission results from heating with concentrated hydrochloric or hydrobromic acids in sealed tubes at 130—140°. A more convenient method of using hydrobromic acid is to heat the phenyl alkyl ether in glacial acetic acid solution with concentrated hydrobromic acid under reflux (Stoermer, *Ber.*, 1908, **41**, 323). The formation of methyl iodide by heating aryl methyl ethers with concentrated hydriodic acid is the basis of the Zeisel method of estimating methyl ethers. Ethoxy groups can be estimated similarly (*Monatsh.*, 1886, **6**, 989).

✓ *Zeisel Method for the Estimation of Methoxyl.*—Concentrated hydriodic acid for use in this estimation should boil constantly at 126° and have *d*, 1·7. It should be free from sulphur and phosphorus compounds.

A 12% solution of silver nitrate is prepared by diluting a solution of 12 g. of silver nitrate in 10 c.c. of water with 90 c.c. of pure alcohol.

The simplest type of apparatus is that described by Perkin (*J.*, 1903, **83**, 1367) (Fig. 5). It consists of a distillation flask *A* with a neck 8″ long between the side arm and the top of the bulb of the flask. The flask is tilted so that the side arm is directed upwards at about 10—15° from the horizontal. The end of the side arm is joined to a small flask *B* containing alcoholic silver nitrate, which in turn is connected to a second flask *C*, also containing silver nitrate. The first flask is so arranged that the delivery tube from the distillation flask is above the surface of the silver nitrate. Connection with the second flask is made through a siphon tube which allows the vapour from the first flask to bubble through the liquid.

For the estimation, a weighed amount of finely-powdered substance (0·15—0·35 g.) is added to 15 c.c. of concentrated hydriodic acid in the decomposition flask, which is now heated in a glycerin bath at 130—140°. During the heating, a steady current of carbon dioxide (about 3 bubbles every 2 seconds) is passed into the decomposition flask. The end of the carbon dioxide delivery tube, *D*, is placed at the top of the bulb of the decomposition flask.

The progress of the decomposition is shown by the density of the turbidity or precipitate in the first flask. As the decomposition proceeds, the temperature of the glycerin bath may be raised so that the hydriodic acid boils gently. The decomposition is complete when the liquid over the precipitate in the first flask remains clear. The operation usually takes 1—2 hours. The contents of the wash flasks are transferred to a beaker, diluted with water, acidified with dilute nitric acid, and gently boiled till most of the alcohol has distilled off. The precipitate of silver iodide is collected, dried, and weighed.

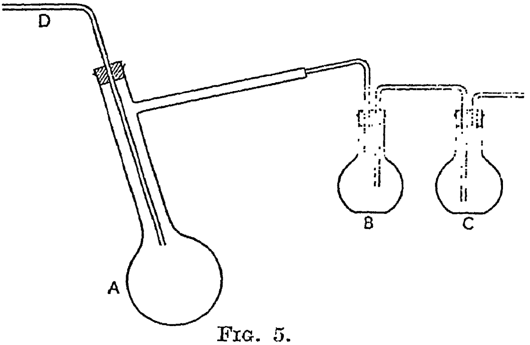


FIG. 5.

A number of different types of apparatus for this estimation have been described. The original papers should be consulted for further particulars (Hewitt and Moore, *J.*, 1902, **81**, 318; W. M. Cumming, *J.S.C.I.*, 1922, **41**, 20; H. Meyer, *Monatsh.*, 1904, **25**, 1213, Stritar, *Z. anal. Chem.*, 1903, **42**, 579.)

It has been found advantageous to add acetic anhydride or acetic acid to the hydriodic acid in this estimation (Baeyer and Villiger, *Ber.*, 1902, **35**, 1199; Hewitt and Moore, *loc. cit.*; Boyd and Pitman, *J.*, 1905, **87**, 1255; Finnemore, *ibid.*, 1908, **93**, 1516). The addition of phenol instead of acetic anhydride has been recommended and can be used with advantage.

A form of apparatus for the Zeisel estimation of methoxyl, which has been developed in the Research Laboratories of the University of Birmingham, and which is suitable for semi-micro-determinations, is represented diagrammatically in Fig. 6.

It consists essentially of a U-tube (*A*) of about 16 mm. internal diameter and the shorter limb about 16 cm. long. To the other limb is fused a fractionating column (*B*), about 18 cm. long, having a small wash flask (*C*) containing water, fused to the side arm. The wash-flask and the fractionating column are closed by corks during the estimation.

The methyl iodide is collected in the filter flasks (*D*, *D*) containing alcoholic silver nitrate.

For the estimation 10—15 cm. of hydriodic acid are used and about 20—20 m.g. of substance having a methoxyl content of 30—40%. Correspondingly larger amounts are used for lower methoxyl contents. The same acid can be used for three or four successive estimations. The general operations are similar to those already described in the preceding account.

Alkyl aryl ethers can be dealkylated by warming with aluminium chloride, and this is an easy method of obtaining the free phenol (Hartmann and Gattermann, *Ber.*, 1892, **25**, 3531).

Demethylation of Anisole by Aluminium Chloride.—Anisole (10 g.) and powdered anhydrous aluminium chloride (15 g.) are mixed. Heat is evolved and a crystalline double compound is formed. It is heated in an open flask for 3 hours at 120°, methyl chloride being evolved. After adding water to the cooled residue, the phenol separates.

*iso*Butyl phenyl ether, *o*-nitroanisole, phenetole, *o*-nitrophenetole, and guaiacol are dealkylated in a similar way.

This process has been modified somewhat by Pfeiffer and Haack (*Annalen*, 1928, **460**, 156), who effect demethylation of aryl methyl ethers by warming with aluminium bromide in purified benzene. According to these authors the probable sequence of reactions is as follows :—

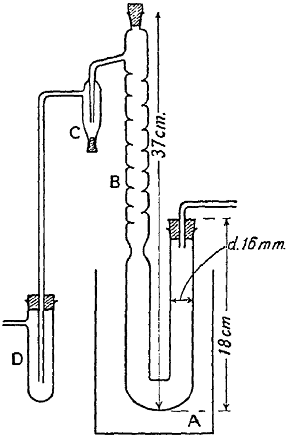


FIG. 6.

$$R{\cdot}OMe \qquad R{\cdot}OMe,AlBr_3 \qquad R{\cdot}O{\cdot}AlBr_2 \xrightarrow{H_2O} R{\cdot}OH$$

The process has been applied not only to the demethylation of aryl alkyl ethers, but also to *p*-methoxyacetophenone and other methoxy-ketones.

Dealkylation of phenol ethers can also be achieved by heating with aniline or *p*-toluidine hydrochlorides (Klemenc, *Ber.*, 1916, **49**, 1371).

The unsubstituted diaryl ethers are comparatively stable to concentrated hydriodic acid; diphenyl ether is stated to be attacked by this reagent at 250° (Hoffmeister, *Ber.*, 1870, **3**, 747). Concentrated sulphuric acid yields sulphonic acids. With concentrated nitric acid substitution takes place in the nucleus. It has been recorded, however, that di-*p*-tolyl ether yields, in addition to the nitrotolyl ethers, appreciable amounts of nitro-cresols formed by the fission of the ether (Reilly, Drumm, and Barrett, *J.*, 1927, 71). Splitting of 4-chloro-2-nitro-4′-methyldiphenyl ether by the action of nitric acid has also been recorded (Fox and E. E. Turner, *J.*, 1930, 1118).

Although ethers are generally stable to alkalis, sodium, or amines, there are some exceptions. Negative substituents such as $-NO_2$, $-CO_2H$, etc., in the nucleus of aryl alkyl ethers render the ether more susceptible to hydrolysis by alkalis. Thus while anisole is split into phenol to the extent of about 12% after heating at 180—200° with twice its weight of alcoholic potash for 15 hours, *o*- and *p*-nitroanisoles are slowly hydrolysed by heating under reflux with aqueous alcoholic caustic soda. The fission of di- and tri-nitroanisoles is effected even more easily by aqueous alkalis. Diphenyl ethers with nitro-groups in *o*- and *p*-positions to the ether oxygen are split by treatment with piperidine, although diphenyl ether itself is indifferent to this reagent (Le Fèvre, Saunders, and E. E. Turner, *J.*, 1927, 1168; Fox and Turner, *loc. cit.*).

Some of the aryl alkyl ethers are decomposed by sodium at high temperatures. Thus β-naphthyl ethyl ether heated to 140° with this metal yields β-naphthol as well as ethyl alcohol, naphthalene, ethane, and ethylene. Phenetole at 200—260° yields phenol and ethyl alcohol (Schorigin, *Ber.*, 1924, **57**, 1627). Benzyl ethers appear to behave abnormally, for the action of sodium wire at 100° on phenyl benzyl ether gives a 30—35% yield of benzhydrol $(Ph)_2CHOH$. Benzyl ethyl ether and naphthyl benzyl ether behave similarly (compare Schorigin, *Ber.*, 1925, **58**, 2028).

The dialkyl ethers have been found to undergo fission by treatment with zinc chloride or ferric chloride and an acyl chloride with the formation of an ester. The reaction is apparently represented by the equation

$$\mathrm{R{\cdot}CO{\cdot}Cl + Et{\cdot}O{\cdot}Et \qquad R{\cdot}CO{\cdot}OEt + EtCl}$$

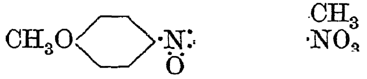
(Descudé, *Compt. rend.*, 1901, **132**, 1129; E. Wedekind and Häussermann, *Ber.*, 1901, **34**, 2081). The scope of the reaction has been extended to cyclic ethers such as cineole and epichlorhydrin (Knoevenagel, *Annalen*, 1914, **402**, 133). It has been suggested as a method of characterising the simple aliphatic ethers. Underwood, Baril, and Toone (*J. Amer. Chem. Soc.*, 1930, **52**, 4087) recommend the following method for this purpose.

Formation of Esters of 3 : 5-Dinitrobenzoic Acid from Aliphatic Ethers.—1 C.c. of the ether is added to 0·1—0·15 g. of finely-powdered anhydrous zinc chloride and 0·5 g. of 3 : 5-dinitrobenzoyl chloride in a test-tube. The mixture is gently heated in an oil-bath so that the ether gently refluxes. After 1 hour the product is poured into a small beaker and the test-tube rinsed out with 10 c.c. of 1·5 *N*-sodium carbonate solution and the washings are added to the reaction mixture. After keeping for 5 minutes at room temperature, the mixture is filtered and the solid washed with 5 c.c. of 1·5 *N*-sodium carbonate solution and then with two separate amounts of 5 c.c. of water. It is drained and then extracted with 10 c.c. of carbon tetrachloride by heating with this solvent at its boiling point for about 3 minutes. The hot mixture is filtered and the filtrate evaporated to dryness. The product thus obtained is the ester of 3 : 5-dinitrobenzoic acid. It is purified by crystallisation from 2—3 c.c. of carbon tetrachloride.

(b) *Addition Compounds of Ethers.*—It has long been known that diethyl ether and dimethyl ether are able to combine additively with hydrogen chloride (Friedel, *Bull. Soc. chim.*, 1875, [ii], **24**, 166, 241) or with $HTlCl_4$ (Nicklès, *Compt. rend.*, 1864, **48**, 537). Further examples of such types of compounds have been described by McIntosh and his collaborators (*J. Amer. Chem. Soc.*, 1908, **30**, 1097; 1912, **34**, 1273; *J.*, 1904, **85**, 919; 1905, **87**, 784), who have prepared additive compounds of the simple dialkyl ethers with halogen hydrides. More recently Tschelinzeff and Kosloff (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 708) have obtained sulphates of diethyl and diamyl ethers which are solid at comparatively low temperatures. Another class of additive compound is formed by the union of ethers with metal halides such as zinc iodide, antimony tribromide, aluminium chloride, aluminium bromide, mercuric bromide, magnesium chloride, etc. Lists of such compounds and references to the original papers are given by Pfeiffer (*Organische Molekülverbindungen*, 1922, p. 43).

The formation of additive compounds is not confined to the dialkyl ethers. Thus cineole forms compounds with ferrocyanic acid, cobalticyanic acid, zinc chloride, cadmium iodide, and also with phenols and organic acids (Baeyer and Villiger, *Ber.*, 1902, **35**, 1205; Pickard and Kenyon, *J.*, 1907, **91**, 900). Additive compounds of alkyl aryl ethers with aluminium chloride, aluminium bromide, and antimony tribromide have also been described (Pfeiffer and Haack, *Annalen*, 1928, **460**, 156; J. W. Walker and A. Spencer, *J.*, 1904, **85**, 1107; Menschutkin, *J. Russ. Phys. Chem. Soc.*, 1904, **44**, 1113).

Highly coloured compounds have been isolated from the products of the action of nitric acid on some alkyl aryl ethers. It has been established that they are represented by the general structure



$$\mathrm{CH_3O\langle\;\rangle{\cdot}\underset{\ddot{O}}{N}{:}\qquad\begin{matrix}\cdot CH_3\\ \cdot NO_3\end{matrix}}$$

The nitrate group may be replaced by others such as perchlorate (Kehrmann and Decker, *Ber.*, 1921, **54**, 2435, 2429; Decker and Solonina, *ibid.*, 1905, **38**, 64; 1902, **35**, 3217; K. H. Meyer and Gottlieb-Billroth, *ibid.*, 1919, **52**, 1476).

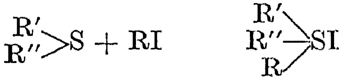
(c) *Nuclear Substitution in the Aryl Ethers.*—In general, the formation of nitro- and sulphonic derivatives of the alkyl aryl and diaryl ethers is brought about by processes similar to those employed for the preparation of the corresponding derivatives of the aromatic hydrocarbons. Bromination and chlorination take place fairly readily; one or two atoms of halogen can be introduced without the aid of a catalyst. If, however, a halogen carrier is present, such as aluminium bromide, all the hydrogens of the nucleus may be substituted readily. The formation of halogen-substituted derivatives can also be brought about by heating the alkyl aryl ether with the appropriate phosphorus pentahalide (Autenrieth and Mühlinghaus, *Ber.*, 1906, **39**, 4100).

These ethers also couple with suitable diazo-compounds to furnish azo-compounds. This reaction is best carried out in acetic acid solution, using a reactive diazo-compound such as those derived by the diazotisation of the mono-, di-, or tri-nitroanilines (K. H. Meyer, Irschick, and Schlösser, *Ber.*, 1914, **47**, 1741). It is noteworthy that some ethers, such as phenyl α-naphthyl ether, suffer a partial fission during this reaction.

(7) *Thioethers.*

Although the thioethers, $\genfrac{}{}{0pt}{}{R}{R'}{>}S$, resemble the oxygen ethers in type, their reactions differ in many respects. The most outstanding differences are the formation of sulphones and sulphoxides by oxidation and of sulphonium salts by the addition of alkyl halides.

The reaction of dialkyl sulphides with alkyl halides takes place when the necessary components are heated together or kept at room temperature for some time. The sulphonium salt separates in a crystalline state (v. Öfele, *Annalen*, 1864, **132**, 82; Cahours, *ibid.*, 1865, **135**, 355).



$$\genfrac{}{}{0pt}{}{R'}{R''}{>}S + RI \qquad \begin{matrix}R'\diagdown\\ R''\!-\!SI\\ R\diagup\end{matrix}$$

The sulphonium halides thus formed are salts which dissolve in water to give a neutral reaction and resemble the quaternary ammonium salts in their reactions. By treatment with moist silver oxide, they are converted into the sulphonium hydroxides; strongly alkaline substances, which take up carbon dioxide from the air and which yield sulphonium salts by neutralisation with acids.

Diaryl sulphides or alkyl aryl sulphides apparently do not react with alkyl halides. Sulphonium salts can, however, be obtained from them by heating with dimethyl sulphate at 100° (Kehrmann and Duttenhöfer, *Ber.*, 1906, **39**, 3559; 1905, **38**, 4197; Kehrmann and Sava, *ibid.*, 1912, **45**, 2895).

Oxidation of the sulphides occurs in two stages. First a sulphoxide is formed, R_2SO, which yields the sulphone by further oxidation. The preparation of the sulphoxide can usually be effected by the action of nitric acid or regulated oxidation with hydrogen peroxide in acetic acid or acetone. An alternative method of less general application consists in the hydrolysis of the corresponding dibromide or dichloride of the sulphide (p. 123).

*Preparation of Di*iso*amyl Sulphoxide.*—(1). Di*iso*amyl sulphide is added to twice its weight of red fuming nitric acid. The solution is afterwards shaken with an excess of sodium carbonate solution. The sulphoxide is precipitated and solidifies on cooling. It is purified by draining on porous earthenware and then crystallising from light petroleum, m.p. 35° (Beckmann, *J. pr. Chem.*, 1878, [ii], **17**, 441).

(2) Di*iso*amyl sulphide (5 g.) in acetone solution is mixed with a slight excess of 30% hydrogen peroxide. After keeping for 24 hours, the solvent is evaporated and the residue crystallised from light petroleum—yield 3 g. (Gazdar and Smiles, *J.*, 1908, **93**, 1834).

Preparation of Diethyl Sulphoxide.—A 30% solution of hydrogen peroxide (5 g.) is added slowly to a mixture of diethyl sulphide (4·5 g.) and an equal weight of acetic acid, which is cooled in a freezing mixture. After keeping for some time, the solvent is evaporated off under reduced pressure and the residue distilled. The sulphoxide is collected at 88—89°/15 mm. and solidifies when cooled in a freezing mixture, m. p. 4—6°.

Some of the corresponding sulphone is also formed. A better yield of this is obtained by increasing the proportion of the oxidising agent.

Preparation of Diethyl Sulphone.—A 30% solution of hydrogen peroxide (6 g.) is slowly added to a cooled mixture of diethyl sulphide (4·5 g.) and acetic acid (4·5 g.). After several weeks the solvent and the sulphoxide are removed by distillation under reduced pressure, leaving a residue of the sulphone, m. p. 73—74° (Pummerer, *Ber.*, 1910, **43**, 1407).

Preparation of Diphenyl Sulphoxide.—Diphenyl sulphide is mixed with 1 mol. prop. of 30% hydrogen peroxide and sufficient acetic acid to give a homogeneous solution. After keeping at room temperature for 4 days, the solution is poured into water and the sulphoxide taken up in chloroform. After washing and drying the chloroform solution, the solvent is evaporated, leaving the sulphoxide, m. p. 70—71° (Hinsberg, *Ber.*, 1910, **43**, 289).

Preparation of Diphenyl Sulphone.—Diphenyl sulphide is mixed in acetic acid solution with 2½ mol. props. of 30% hydrogen peroxide. The separation of crystals of the sulphone commences after keeping for several days. It is then precipitated by the addition of water, filtered off, and crystallised from alcohol, m. p. 128° (Hinsberg, *loc. cit.*).

Preparation of Thionyldiglycollic Acid, $SO(CH_2{\cdot}CO_2H)_2$.—A solution of thiodiglycollic acid in an excess of aqueous hydrogen peroxide is kept at room temperature for 48 hours, when the excess of water is evaporated. The syrupy residue kept in a vacuum desiccator gradually furnishes crystals of thionyldiglycollic acid, m. p. 79—80° (Gazdar and Smiles, *loc. cit.*).

Preparation of Sulphonal, $(CH_3)_2C(SO_2Et)$.—Acetone diethyl mercaptal, $(CH_3)_2C(SEt)_2$, is shaken with a 5% aqueous solution of permanganate and a few drops of acetic or sulphuric acid are added from time to time. When there is no further reduction of the permanganate, the solution is heated to boiling, the excess of oxidising agent destroyed by the addition of alcohol and then filtered hot. On evaporating the filtrate to half its bulk, sulphonal separates out, m. p. 125° (Baumann, *Ber.*, 1886, **19**, 2808).

Preparation of Sulphones from 2 : 4-Dinitrophenyl Thioethers.—A 3% aqueous solution of permanganate (in 50% excess of theoretical) is added to a saturated solution of 0·01 g.-mol. of the thio ether in glacial acetic acid. When all the oxidising agent has been added, the excess is decolorised by passing sulphur dioxide. The sulphone is precipitated by the addition of ice. It is recrystallised from absolute alcohol (Bost, J. O. Turner, and Norton, *J. Amer. Chem. Soc.*, 1932, **54**, 1986).

Permanganate is fairly widely used for the oxidation of sulphides to sulphones, and for this purpose it is advantageous to use acetic acid as a solvent for the sulphide (Otto, *Ber.*, 1880, **13**, 1272; Beckmann, *loc. cit.*).

The addition of chlorine, bromine, or iodine to the sulphur atom

TABLE V.

	B. p.	M. p.	Acetate. B. p.	Formate. B. p.	Propionate. B. p.	*n*-Butyrate. B. p.	*iso*Butyrate. B. p.	*iso*Valerate. B. p.	Benzoate. B. p.
Methyl alcohol . .	65°	—	57°	32°	80°	102°	93°	116°	199°
Ethyl alcohol . .	78	—	77	54	99	116	110	134	212
*iso*Propyl alcohol . .	82	—	91	70	110	128	120	142	219
tert.-Butyl alcohol . .	82	25	95	—	—	—	—	—	—
n-Propyl alcohol . .	97	—	101	81	122	142	134	156	229
Allyl alcohol . . .	97	—	103	—	124	142	—	—	230
sec.-Butyl alcohol . .	100	—	112	—	132	—	—	163	234
*iso*Butyl alcohol . .	108	—	116	99	137	157	147	168	234
tert.-Amyl alcohol . .	102	—	—	—	—	—	—	—	—
a-Ethylpropyl alcohol .	112	—	—	—	—	—	—	—	—
n-Butyl alcohol . .	117	—	125	107	145	165	—	—	247
Glycol monomethyl ether	125	—	145	—	—	—	—	—	254
β-Methylbutyl alcohol .	128	—	141	—	—	—	—	—	—
β-Chloroethyl alcohol .	130	—	145	—	—	—	—	—	254
γ-Methylbutyl alcohol .	130	—	139	124	160	170	169	188	260
δ-Methylbutyl alcohol .	131	—	159	—	—	—	—	—	—
Glycol monoethyl ether .	134	—	158	—	—	—	—	—	—
n-Amyl alcohol . .	138	—	148	—	—	—	—	—	—
β-Bromoethyl alcohol .	148	—	163	—	—	—	—	—	280
βββ-Trichloroethyl alcohol	150	18	170	—	—	—	—	—	—
n-Hexyl alcohol . .	157	—	169	154	208	205	—	—	272
*cyclo*Hexanol . . .	160	—	176	162	193	212	204	233	192/61
2-Methyl*cyclo*hexanol .	165	—	182	173	203	221	212	231	200/55
3-Methyl*cyclo*hexanol .	172	—	185	176	206	224	215	234	[66]
4-Methyl*cyclo*hexanol .	174	—	188	177	207	225	216	235	—
Pinacone . . .	172	35	—	—	—	—	—	—	—
Capryl alcohol . .	180	—	193	186	—	—	—	—	—
Propylene glycol . .	188	—	186	—	—	—	—	—	240
n-Octyl alcohol . .	196	—	210	198	226	—	—	—	—
Ethylene glycol . .	197	—	186	—	—	—	—	—	[73]
Linalool . . .	197	—	—	—	—	—	—	—	—
Benzyl alcohol . .	205	—	216	—	219	238	228	136/25	[21]
l-Menthol . . .	212	42	227	215	118/ 15 mm.	126/ 13 mm.	116/ 12 mm.	125/ 10 mm.	[54]
a-Terpineol . . .	212	—	—	—	—	—	—	—	—
Trimethylene glycol .	216	—	209	—	—	—	—	—	[54]
Phenyl ethyl alcohol .	219	—	232	—	—	—	—	—	—
Citronellol . . .	222	—	—	—	—	—	—	—	—
Glycerol . . .	290	[180/° 20 mm.]	—	—	—	—	—	—	[76]
Cinnamyl alcohol . .	250	33	—	—	250	—	—	—	—
Cetyl alcohol . . .	—	48	[22]	—	—	—	—	—	[30]
Diphenyl carbinol . .	298	68	[41]	—	—	—	[54]	—	—
Myricyl alcohol . .	—	88	[73]	—	—	—	—	—	[70]
Triphenyl carbinol . .	—	163	—	—	—	—	—	—	—
Mannitol . . .	—	166	[119]	—	—	—	—	—	[149]
Dulcitol . . .	—	188	[171]	—	—	—	—	—	[147]
Sorbitol (anhydrous) .	—	*circa.* 110	syrup	—	—	—	—	—	—
Borneol . . .	—	209	—	—	—	—	—	—	[26]
Inositol . . .	—	225	[215]	—	—	—	—	—	—

[ ] in a column headed B. p. indicate that the substance is solid. The figures within the brackets give the m. p.

Conversely, in a column headed M. p. the figures within the brackets give the b. p. of a liquid.

Alcohols.

p-Nitro-benzoate. M. p.	3 : 5-Dinitro-benzoate. M. p.	Phenyl urethane. M. p.	α-Naphthyl urethane. M. p.	*p*-Nitrophenyl urethane.(*a*) M. p.	*p*-Xenyl urethane.(*b*) M. p.	Ester of anthra-quinone β-carb-oxylic acid. M. p.	
96	109	47	124	179	127	167	
57	93	52	79	129	119	148	
110	122	90	78	116	138	141	
—	143	—	—	—	—	—	
35	73	58	105	115	129	116	
—	50	—	—	—	—	160	
—	75	—	97	75	—	—	
—	87	80	104	80	—	121	
—	118	—	—	—	—	99	
—	—	—	—	—	—	—	
—	63	oil	71	96	109	123	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	61	55	67	98	—	89	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	61	—	59	103	—	89	
—	113	82	—	—	166	117	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	Fuming HBr → Tetramethylethylene dibromides. Dist. with I → butadiene.
—	32	114	63	oil	—	51	
—	—	—	—	—	—	—	
—	61	—	—	—	—	86	
—	—	157	176	136	—	—	
—	—	64°	—	—	—	—	
316	—	—	—	—	—	—	
61	151	112°	—	—	—	—	Gentle oxidation with CrO_3 → menthone.
—	—	110°	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	Rose-like odour.
192	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	Intense brown coloration with H_2SO_4.
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
—	—	—	—	—	—	—	
137	—	—	—	—	—	—	
—	—	—	—	—	—	—	Evaporation with dil. HNO_3 on water-bath, solution of dry residue in water and addition of little Sr acetate → violet coloration.

(*a*) Morgan and Pettet, *J.*, 1931, 1125.
(*b*) Shriner and Cox, *J. Amer. Chem. Soc.*, 1931, **53**, 1601; for other derivatives see Nicolet and Sacks, *ibid.*, 1925, **47**, 2348.

TABLE VI.

Phenols.

	M. p.	B. p.	Acetate. M. p.	Benzoyl derivative. M. p.	Benzene-sulphonyl derivative. M. p.	*p*-Toluene-sulphonyl derivative. M. p.	Aryloxy-acetic acid. M. p.	Colour with ferric chloride.	
o-Bromophenol	—	194°	[150°/ 35 mm.]	213°	—	—	141°	—	*p*-Nitrobenzyl ether, m. p. 110°.
3-Chloro-*p*-cresol	—	196	—	—	—	—	108	—	
m-Cresol	—	202	[212]	54	45°	50°	102	Blue	*p*-Nitrobenzyl ether, m. p. 51°; 3 : 5-dinitrobenzoate, m. p. 165°.
3-Bromo-*p*-cresol	—	214	—	—	—	—	—	—	
Carvacrol	0°	237	[246]	—	—	—	150	Green (alc.)	3 : 5-Dinitrobenzoate, m. p. 76°; nitroso-derivative, m. p. 153°.
Resorcinol monomethyl ether	—	244	—	—	—	—	112	—	
Eugenol	—	254	31	69	—	85	—	—	*p*-Nitrobenzyl ether, m. p. 54°; 3 : 5-dinitrobenzoate, m. p. 131°.
*iso*Eugenol	—	261	79	103	—	—	—	Olive green (alc.)	3 : 5-Dinitrobenzoate, m. p. 158°.
4-Hydroxy-3-methoxytoluene	5	222	—	—	—	—	—	—	
o-Chlorophenol	7	175	[103°/ 15 mm.]	—	—	—	145	—	*p*-Nitrobenzyl ether, m. p. 101°; carbanilate, m. p. 120°.
4-Hydroxy-*m*-xylene	26	211	—	39	—	—	—	Blue	3 : 5-Dinitrobenzoate, m. p. 165°; carbanilate, m. p. 102°.
m-Chlorophenol	29	214	[117°/ 21 mm.]	71	—	—	—	—	
o-Cresol	30	191	[208]	—	39	55	151	Blue	*p*-Nitrobenzyl ether, m. p. 90°; 3 : 5-dinitrobenzoate, m. p. 138°.
Guaiacol	32	205	[235]	57	51	85	116	Green (alc.)	3 : 5-Dinitrobenzoate, m. p. 141°; carbanilate, m. p. 136°. 1 c.c. guaiacol diss. in 60 c.c. water at 15°.
m-Bromophenol	33	236	[149°/ 40 mm.]	86	—	—	108	—	
3-Nitro-*p*-cresol	34	—	—	102	—	—	—	—	
p-Cresol	36	200	[208]	71	43	69	135	Blue	*p*-Nitrobenzyl ether, m. p. 88°; 3 : 5-dinitrobenzoate, m. p. 187°.
3 : 5-Dichloro-*p*-cresol	39	—	—	—	—	—	—	—	
p-Chlorophenol	41	217	[228]	86	—	—	155	—	Nitration yields 4-chloro-2-nitrophenol and subsequently 4-chloro-2 : 6-dinitrophenol.
Phenol	43	181	[195]	69	35	95	99	Violet	*p*-Nitrobenzyl ether, m. p. 91°; 3 : 5-dinitrobenzoate, m. p. 146°.
2 : 4-Dichlorophenol	43	209	[244]	97	—	—	—	—	
o-Nitrophenol	44	—	39	59	75	81	—	—	

5-Chloro-*o*-cresol	48	—	—	71	—	—	—	—	Sulphur-yellow needles, decomposes Na_2CO_3.
3 : 5-Dibromo-*p*-cresol	49	—	—	—	—	—	—	—	
2-Hydroxy-*m*-xylene	49	—	—	—	—	—	—	—	3 : 5-Dinitrobenzoate, m. p. 159°.
Thymol	51	232	[244]	32	55	—	149	Green (alc.)	*p*-Nitrobenzyl ether, m. p. 86°; 3 : 5-*dinitro*benzoate, m. p. 130°.
Quinol monomethyl ether	53	243	—	—	—	—	111	—	
3 : 5-Dichloro-*o*-cresol	54	—	—	—	—	—	—	—	
5-Bromothymol	56	—	—	—	—	—	—	—	
3 : 5-Dibromo-*o*-cresol	56	—	—	—	—	—	—	—	
4-Nitro-*m*-cresol	56	—	—	—	—	—	—	—	
2 : 5-Dichlorophenol	58	211	—	—	—	—	—	—	
ar-Tetrahydro-*β*-naphthol	59	275	—	—	—	—	—	Blue-green	
p-Hydroxy-*o*-xylene	62	225	—	58	—	—	—	Blue	3 : 5-Dinitrobenzoate, m. p. 182°.
5-Hydroxy-*m*-xylene	64	220	—	24	—	—	—	None	3 : 5-Dinitrobenzoate, m. p. 195°.
*homo*Pyrocatechol	65	251	—	—	—	—	—	Green	
p-Bromophenol	64	236	21	102	—	—	157	—	Carbanilate, m. p. 144°.
2 : 3 : 5-Trichlorophenol	66	—	—	80	—	—	—	—	
6-Chloro-*m*-cresol	66	—	—	—	—	—	—	—	
2 : 4 : 6-Trichlorophenol	67	—	[261]	70	66	—	—	—	
Mesitol	68	—	—	—	—	—	—	None	
ar-Tetrahydro-*α*-naphthol	69	264	—	—	—	—	—	—	
ψ-Cumenol	70	230	—	63	—	—	—	None	
2 : 4-Di-iodophenol	72	—	72	—	—	—	—	—	
p-Xylenol	74	212	[237]	61	51	—	—	None	3 : 5-Dinitrobenzoate, m. p. 137°; carbanilate, m. p. 160°.
4-Bromo-2 : 6-dinitrophenol	76	—	164	—	—	—	—	—	
3 : 5 : 6-Tribromo-*o*-cresol	79	—	—	—	—	—	—	—	
3 : 5-Dinitro-*p*-cresol	80	—	—	—	—	—	—	—	
4-Chloro-2 : 6-dinitrophenol	81	—	—	—	—	—	—	—	
2 : 4 : 6-Tribromophenol.	83	—	—	—	—	—	—	—	
4-Chloro-2-nitrophenol	86	—	47	—	—	—	—	—	
3 : 5-Dinitro-*o*-cresol	86	—	—	—	—	—	—	—	
4-Bromo-2-nitrophenol	88	—	—	—	—	—	—	—	
3 : 4 : 6-Tribromo-*p*-xylenol	90	—	—	—	—	—	—	—	
p-Iodophenol	92	—	32	119	52	—	154	—	Carbanilate, m. p. 168°.
2 : 4 : 6-Tribromophenol.	96	—	82	81	99	—	—	—	
m-Nitrophenol	96	—	—	95	72	—	—	—	
α-Naphthol	94	280	46	56	—	—	191	*	3 : 5-Dinitrobenzoate, m. p. 217°; *p*-nitrobenzyl ether, m. p. 140°; carbanilate, m. p. 178°.
2 : 3 : 5-Tribromo-*p*-cresol	96	—	72	—	—	—	—	—	
tert.-Butylphenol	99	236	[246]	83	—	—	—	—	
3 : 5 : 6-Trinitro-*o*-cresol.	102	—	—	—	—	—	—	—	
4-Methylresorcinol	104	267	[293]	—	—	—	—	Blue	
Chloroquinol	104	263	71	130	—	—	—		
Catechol	105	245	64	84	—	—	—	Emerald-green	with $FeCl_3$ → dark red to violet on adding $NaHCO_3$. 100 g. sat. sol. contains 31 g.
Orcinol	108	287	25	88	—	—	—	—	
2 : 4 : 6-Trinitro-*o*-cresol.	110	—	—	140	—	—	—	—	

TABLE VI—*continued.*

Phenols.

	M. p.	B. p.	Acetate. M. p.	Benzoyl derivative. M. p.	Benzene-sulphonyl derivative. M. p.	*p*-Toluene-sulphonyl derivative. M. p.	Aryloxy-acetic acid. M. p.	Colour with ferric chloride.	
Resorcinol	110	276	[273]	117	69	81	—	Dark violet.	100 g. water dissolve 147 g. at 12·5°; 86·4 at 0°.
Bromoquinol	110	—	71	—	—	—	—	—	
4 : 6-Dibromoresorcinol	110	—	—	—	—	—	—	—	
2 : 4 : 6-Tribromoresorcinol	111	—	—	—	—	—	—	—	
2 : 4-Dinitrophenol	113	—	72	132	118	121	—	—	
p-Nitrophenol	114	—	82	142	82	97	—	—	
6-Bromo-2 : 4-dinitrophenol	118	—	—	128	—	—	—	—	
5-Nitro-*o*-cresol	118	—	—	128	—	—	—	—	
Picric acid	122	—	75	163	—	—	—	—	
β-Naphthol	123	285	70	106	107	125	153	Faint green → white ppt.	*p*-Nitrobenzyl ether, m. p. 106°; carbanilate, m. p. 155°.
Toluquinol	124	—	51	—	—	—	—	—	
m-Xyloresorcinol	125	—	45	—	—	—	—	—	
Pyrogallol	133	293	161	89	141	—	—	—	
Thymoquinol	140	290	80	—	—	—	—	—	
3 : 6-Dibromo-5-hydroxy-1 : 2 : 4-trimethylbenzene	149	—	81	—	—	—	—	—	
2 : 4 : 6-Tri-iodophenol	156	—	156	137	155	—	—	—	
2 : 3-Dihydroxynaphthalene	160	—	—	—	—	—	—	Intense dark blue	
2 : 7-Dihydroxynaphthalene	165	—	129	—	—	—	—	—	
2 : 5-Dichloroquinol	170	—	141	—	—	—	—	—	
Quinol	170	—	124	199	120	—	—	—	100 g. sat. sol. contain 5·8 g. at 15°; 9·4 g. at 28·5°.
2 : 4 : 6-Trinitroresorcinol	175	—	—	—	—	—	—	—	
2 : 5-Dibromoquinol	186	—	161	—	—	—	—	—	
p-Xyloquinone	213	—	—	—	—	—	—	—	
2 : 6-Dihydroxynaphthalene	215	—	175	—	—	—	—	Yellowish-white ppt. → green with alkali.	
Phloroglucinol	218	—	105	173	116	—	—	Brown → violet-red with Na_2CO_3.	
Tetrachloroquinol	232	—	—	—	—	—	—	—	
Tetrabromoquinol	244	—	—	—	—	—	—	—	
1 : 5-Dihydroxynaphthalene	260	—	—	—	—	—	—	—	

* White turbidity with $FeCl_3$ changing through red to violet with the formation of a violet ppt.

[ ] in a column headed B. p. indicate that the substance is solid. The figures within the brackets give the m. p. Conversely, in a column headed M. p. the figures within the brackets give the b. p. of a liquid.

TABLE VII.

Mercaptans.

	B. p.	M. p.	Hg salt.(*a*) M. p.	3 : 5-Dinitro-benzo-ate.(*a*) M. p.	3-Nitro-phthalic acid ester.(*a*) M. p.	Disul-phide. M. p.	2 : 4-Dinitro-phenyl sulphide.(*b*) M. p.	2 : 4-Dinitro-phenyl sul-phone.(*b*) M. p.	
Methyl mercaptan	6°	—	175°	—	—	[110]°	128°	190°	
Ethyl mercaptan	36	—	76	62°	149°	[153]	115	160	Pb salt, m. p. 150°
n-Propyl mercaptan	67	—	72	52	136	—	81	128	
*iso*Butyl mercaptan	88	—	95	64	135	—	76	106	
n-Butyl mercaptan	97	—	86	49	143	—	66	92	Pb salt, m. p. 81°
*iso*Amyl mercaptan	117	—	100	43	144	—	59	95	
Thiophenol	169	—	—	149	130	62	121	161	
Benzyl mercaptan	194	—	—	120	136	71	130	183	
Thio-*o*-cresol	194	15	—	—	—	38	—	—	
Thio-*p*-cresol	195	43	—	—	—	46	103	190	
Thio-*m*-cresol	200	—	—	—	—	[174/ 12 mm.]	—	—	
2 : 4-Dimethylthiophenol	207	—	—	—	—	—	—	—	
Thio-α-naphthol	209	—	—	—	—	85	—	—	
p-Chlorothiophenol	—	53	—	—	—	88	—	—	
p-Bromothiophenol	—	74	—	—	—	113	—	—	
Thio-β-naphthol	286	81	—	—	—	139	—	—	

(*a*) Wertheim, *J. Amer. Chem. Soc.*, 1929, **51**, 3662.
(*b*) Bost, Turner, and Norton, *ibid.*, 1932, **54**, 1985.
[ ] indicate that the disulphide is liquid.
The figures within the brackets give the b. p.

TABLE VIII.

Ethers.

	B. p.	M. p.	*d.*	
Diethyl ether	35°	—	$0{\cdot}7199^{15}_{15}$	
Methylal	42	—	$0{\cdot}872^{15}_{4}$	Hydrolysed by dil. acid
Ethyl *n*-propyl ether	63	—	$0{\cdot}7400^{14{\cdot}3}_{0}$	
Di*iso*propyl ether	69	—	$0{\cdot}7247^{21}_{0}$	
Formaldehyde diethyl ether	87	—	—	” ” ” ”
Di-*n*-propyl ether	91	—	$0{\cdot}7443^{20}_{0}$	
Acetal	102	—	—	” ” ” ”
Di*iso*butyl ether	122	—	$0{\cdot}762^{15}$	
Paraldehyde	124	—	—	” ” ” ”
Di-*n*-butyl ether	141	—	$0{\cdot}7685^{20}_{0}$	
Anisole	154	—	$0{\cdot}990^{22}_{4}$	Nitration to mono-, di-, and tri-nitro-derivatives
*para*Propionaldehyde	170	—	—	Hydrolysed by dil. acid
Phenetole	170	—	$0{\cdot}970^{15}_{15}$	Nitration to mono-, di-, and tri-nitro-derivatives
Methyl *o*-tolyl ether	171	—	$0{\cdot}985^{15}_{15}$	
Di*iso*amyl ether	172	—	$0{\cdot}781^{15}_{15}$	
Methyl *m*-tolyl ether	177	—	$0{\cdot}985^{4}_{4}$	Trinitro-derivative, m. p. 91°. Aq. $KMnO_4 \longrightarrow$ *m*-methoxybenzoic acid
Methyl *p*-tolyl ether	175	—	$0{\cdot}984^{4}_{4}$	Dinitro-derivative, m. p. 122°. CrO_3 and $H_2SO_4 \longrightarrow$ anisic acid
Ethyl benzyl ether	188	—	—	
Allyl phenyl ether	192	—	$0{\cdot}985^{15}_{15}$	Geranium-like odour
Benzaldehyde dimethyl-acetal	198	—	—	Hydrolysed by dil. acid
Benzaldehyde diethyl-acetal	222	—	—	” ” ” ”
*iso*Amyl phenyl ether	225	—	$0{\cdot}920^{22}_{4}$	
Diphenyl ether	252	27	—	4-Nitrodiphenyl ether, m. p. 61°. 4 : 4′-Dinitrodiphenyl ether, m. p. 141°
Methyl *α*-naphthyl ether	269	—	$1{\cdot}096^{14}_{4}$	Red picrate
Ethyl *α*-naphthyl ether	276	5	$1{\cdot}064^{15}_{15}$	Excess HNO_3 at 0° ⟶ 2 : 4 : 5-trinitro-, m. p. 150°
Methyl *β*-naphthyl ether	274	72	—	Orange-blossom odour. Regulated nitration ⟶ 1-nitro-derivative, m. p. 128°
Ethyl *β*-naphthyl ether	282	37	—	Odour similar to Me ether. Regulated nitration ⟶ 1-nitro-derivative, m. p. 103°, with some 6-nitro- and 8-nitro-ethyl-*α*-naphthyl ether
ββ-Dinaphthyl ether	—	105	—	Orange-red picrate, m. p. 122°
αα-Dinaphthyl ether	—	110	—	
Dibenzyl ether	295	—	—	
Metaldehyde	—	—	—	Sublimes on heating
Metapropionaldehyde	—	—	—	Sublimes about 160°
Trioxymethylene	—	—	—	Sublimes on heating

For the identification of aliphatic ethers by reaction with 3 : 5-dinitrobenzoyl chloride, see p. 112.

TABLE IX.

Sulphides.

	B. p.	M. p.	*d.*	Sulph-oxide. M. p.	Sul-phone. M. p.	
Dimethyl sulphide	37°	—	$0{\cdot}870^{0}_{4}$		109°	
Diethyl sulphide	92	—	$0{\cdot}837^{20}_{4}$	syrup	70	
Di-*n*-propyl sulphide	142	—	—	15°	29	
Di-*n*-butyl sulphide	182	—	—	32	43	
Methyl phenyl sulphide	188	—	—	—	88	
Ethyl phenyl sulphide	204	—	$1{\cdot}024^{15}_{4}$	—	41	
Diphenyl sulphide	295	—	$1{\cdot}127^{7}_{4}$	70	124	Odourless.
Dibenzyl sulphide	—	49°	—	133	151	
Di-*p*-tolyl sulphide	—	56	—	92	158	
Di-$\alpha\alpha$-naphthyl sulphide	—	110	—	166	187	
Di-$\beta\beta$-naphthyl sulphide	—	151	—	—	177	

of thioethers occurs more or less readily. In general, these additive compounds, which are of the type $R_2S{\cdot}Br_2$, tend to lose the halogen. With water, many of the dichlorides and dibromides yield sulphoxides; the hydrolysis takes place, however, more conveniently with dilute alkali.

$$R_2SBr_2 + H_2O \longrightarrow R_2SO + 2HBr$$

The stability of the dibromides appears to be determined, to some extent, by the groups attached to the sulphur. Thus the sulphides with a methyl or methylene adjacent to the sulphur form halogen additive compounds fairly readily (Fromm and Raiziss, *Annalen*, 1910, **374**, 90), while diphenyl sulphide, by addition of bromine in carbon tetrachloride at − 10°, forms a dibromide which is converted into 4-bromodiphenyl sulphide at room temperature. Diphenyl sulphide dichloride is converted into the corresponding sulphone by exposure to moist air (Fries and Vogt, *Annalen*, 1911, **381**, 341; compare Zincke and Frohneberg, *Ber.*, 1909, **42**, 2723; 1910, **43**, 843). A very large number of additive compounds of the thioethers with metal salts are known. A full list of such compounds and references to the original literature are given by Pfeiffer (*Organische Molekülverbindungen*, 1922, pp. 125—130).

CHAPTER IV

ALDEHYDES AND KETONES

- (1) General Reactions.
    - (*a*) Additive Reactions.
        - 1. With Bisulphite.
        - 2. With Hydrogen Cyanide.
        - 3. Amines and Ammonia.
    - (*b*) Reduction of the Carbonyl Group.
        - 1. Formation of Alcohols.
        - 2. Reduction of $>CO$ to $>CH_2$.
    - (*c*) Reaction of the Carbonyl Group with Ammonia and Compounds containing the $R{\cdot}NH_2$ Grouping.
        - 1. Amines and Ammonia.
        - 2. Hydrazine and its Derivatives.
        - 3. Hydroxylamine.
        - 4. Effect of Configuration on the Reaction with Hydrazines and Hydroxylamine.
    - (*d*) Reaction of Aldehydes and Ketones with the Methylene Group.
        - 1. Of Aldehydes and Ketones.
        - 2. Of Nitroparaffins and Nitriles.
        - 3. Of Esters and Acids.
    - (*e*) Reaction with the Grignard Reagent.
    - (*f*) Formation of Acetals.
    - (*g*) Formation of Diacyl Derivatives.
    - (*h*) Enolisation.
- (2) Special Reactions of Aldehydes.
    - (*a*) Oxidation.
    - (*b*) Cannizzaro Reaction.
    - (*c*) Acyloin Condensation.
    - (*d*) Doebner's Reaction.
    - (*e*) Polymerisation.
    - (*f*) Reaction with Diazomethane.
    - (*d*) Formation of *iso*Nitroso Ketones.
- (3) Special Reactions of Ketones.
    - (*a*) Alkylation.
    - (*b*) Fission.
    - (*c*) Internal Condensation of Alkylbenzophenones.
- (4) Special Reactions of Dicarbonyl Compounds.
    - (*a*) 1 : 2-Diketones.
    - (*b*) 1 : 3-Diketones.
    - (*c*) 1 : 4-Diketones.
- (5) Hydroxy Aldehydes and Ketones. Carbohydrates.
    - (*a*) α-Hydroxy Aldehydes and Ketones.
    - (*b*) β-, γ-, and δ-Hydroxy Aldehydes and Ketones.
    - (*c*) Reducing Sugars.
        - 1. Oxidation.
        - 2. Action of Phenylhydrazine.
        - 3. Reactions as Alcohols.
        - 4. γ-Sugars.

(6) Quinones.
    (*a*) Reduction.
    (*b*) Formation of Substituted Quinones and Quinols.
    (*c*) Reactions as Ketones.
    (*d*) Formation of Quinhydrones.
    (*e*) Estimation.

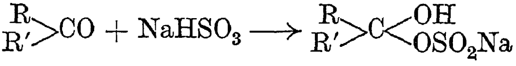
(1) *General Reactions.*

(a) *Additive Reactions.*

Aldehydes and ketones can be represented by the general formula R·CO·R′. In the ketones both R and R′ represent hydrocarbon residues, in the aldehydes R′ = H. Since both classes of compound have a carbonyl group, it is clear that they will have many reactions in common.

Although many of the reactions of the carbonyl group may be considered to be dependent on the formation of addition compounds, it is proposed in this section to restrict the discussion to those which can be represented as formed by the direct union of the carbonyl group with molecules of the reagent employed. Reactions other than these are considered later.

1. *Addition of Bisulphite.*—The carbonyl group can combine with bisulphites to give salts of the sulphurous esters of α-hydroxy alcohols according to the scheme :—



$$\begin{matrix}R\\R'\end{matrix}\!>\!CO + NaHSO_3 \longrightarrow \begin{matrix}R\\R'\end{matrix}\!>\!C\!<\!\begin{matrix}OH\\OSO_2Na\end{matrix}$$

These substances are in general crystalline solids, sparingly soluble in bisulphite solutions, and which separate out in a solid state by the addition of an excess of bisulphite solution to a suitable carbonyl compound. Their formation supplies a convenient method of separating carbonyl compounds from mixtures with other substances, and it has the further advantage that the aldehyde or ketone can readily be liberated from the bisulphite compound by distillation with aqueous sodium carbonate or dilute acid.

Most aldehydes form bisulphite compounds, although there are exceptions, such as phenyldimethylacetaldehyde, diphenylethylacetaldehyde (Tiffeneau and Dorlencourt, *Compt. rend.*, 1906, **143**, 1242), and the aldehydes derived from thymol and carvacrol (Kobek, *Ber.*, 1883, **16**, 2097; Nordmann, *ibid.*, 1884, **17**, 2634). The ease of formation of bisulphite compounds from ketones depends on the configuration. Ketones of the type CH_3·CO·R, where R is a primary alkyl grouping, react comparatively readily, but where R is a secondary or tertiary alkyl group there is some resistance to the addition. Aliphatic ketones of the type R·CO·R′, R and R′ being ethyl or higher alkyl groups, do not readily combine with bisulphite. Further, aromatic and mixed aromatic aliphatic ketones show no tendency to yield bisulphite compounds. On the other hand, *cyclo*hexanone and similar cyclic ketones readily form additive compounds with bisulphite (compare Petrenko-Kritschenko, *Annalen*, 1905, **341**, 163; A. W. Stewart, *J.*, 1905, **87**, 186). The reaction of unsaturated ketones with bisulphite has already been referred to (p. 23).

2. *Addition of Hydrogen Cyanide.*—The reaction of the carbonyl group with hydrogen cyanide results in the formation of an α-hydroxy nitrile according to the scheme

$$>CO + HCN \longrightarrow >C(OH)CN.$$

This reaction appears to be a reversible one, the position of equilibrium being largely in favour of cyanohydrin formation. Other factors influencing the addition are the configuration of the carbonyl compound and the nature of the solvents, water having apparently a dissociating effect on cyanohydrins (W. J. Jones, *J.*, 1914, **105**, 1560; Ultèe, *Rec. trav. chim.*, 1909, **28**, 1, 248, 257; Lapworth and Manske, *J.*, 1928, 2533; 1930, 1976).

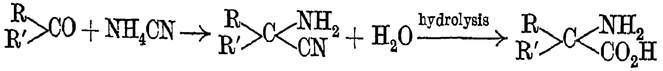
The preparation of cyanohydrins may be brought about quite simply by mixing the aldehyde or ketone with anhydrous hydrogen cyanide. A more satisfactory and more generally applicable process, however, based on the theoretical considerations of Lapworth (*J.*, 1903, **83**, 1000), has been developed by Ultèe (*loc. cit.*). The carbonyl compound is mixed with 10—20% excess of anhydrous hydrogen cyanide, and a trace of potassium cyanide or of an alkaline solution added. The mixture becomes warm and, after cooling, the catalyst is neutralised with the necessary amount of sulphuric acid. The excess of hydrogen cyanide is removed on the water-bath and the cyanohydrin distilled under reduced pressure.

Convenient methods for the preparation of cyanohydrins which obviate the necessity of using anhydrous hydrogen cyanide have been described. Bucherer and Grolée (*Ber.*, 1906, **39**, 1224) add the requisite amount of an aqueous solution of potassium cyanide to a stirred and cooled suspension of the bisulphite compound. The cyanohydrin is isolated by extraction with ether when the reaction is complete. A somewhat similar process is described by Albert (*Ber.*, 1916, **49**, 1382).

Welch and Clemo have recently described a simple method of preparing acetone cyanohydrin (*J.*, 1928, 2629).

Preparation of Acetone Cyanohydrin.—Acetone (29 g.) is added to a solution of potassium cyanide (31 g.) in 100 c.c. of water and the solution cooled. To this solution, which is stirred, are added slowly 167 g. of 30% aqueous sulphuric acid, and the reaction mixture is kept below 20° by the addition of ice. The cyanohydrin is isolated by three extractions with ether, and the ethereal solution after drying over sodium sulphate is distilled under reduced pressure. The acetone cyanohydrin (32 g.) is collected at 81°/15 mm.

Somewhat similar in type to the addition of hydrogen cyanide is the reaction of aldehydes and ketones with ammonium cyanide. An amino-nitrile is formed.



$$\overset{R}{\underset{R'}{}}\!\!>CO + NH_4CN \rightarrow \overset{R}{\underset{R'}{}}\!\!>C<\overset{NH_2}{\underset{CN}{}} + H_2O \xrightarrow{\text{hydrolysis}} \overset{R}{\underset{R'}{}}\!\!>C<\overset{NH_2}{\underset{CO_2H}{}}$$

The reaction has been employed for the preparation of amino-acids through the intermediate formation of the amino-nitrile from acetone, acetaldehyde, propaldehyde, benzaldehyde, *cyclo*hexanone, and other cyclic ketones (Zelinski and Stadnikoff, *Ber.*, 1906, **39**, 1725; 1908, **41**, 2063).

Preparation of Phenylaminoacetic Acid.—Benzaldehyde (5 g.) is added to potassium cyanide (3 g.) and ammonium chloride (2·5 g.) dissolved in the smallest amount of water, and then sufficient methyl alcohol to give a clear solution. The solution soon becomes turbid, and after 3 hours at room temperature the separation of the oil is complete. It is taken up in ether, the ethereal solution washed with water, and the solvent then evaporated under reduced pressure. The residue is treated with 10% hydrochloric acid and any undissolved oil removed by extraction with ether. The aqueous acid solution deposits crystals of the hydrochloride of the amino-nitrile.

Hydrolysis of the nitrile is effected by dissolving the hydrochloride in fuming hydrochloric acid, and after keeping overnight, the solution is diluted with an equal volume of water and heated to boiling. Phenylaminoacetic acid is precipitated by neutralising with dilute ammonia. It is purified by crystallisation from aqueous formic acid, m. p. 255°.

3. *The Addition of Ammonia and Amines* is discussed on pp. 133 and 134.

(b) *Reduction of the Carbonyl Group.*

1. *Formation of Alcohols.*—The use of sodium or sodium amalgam has been extensively applied for the reduction of ketones to secondary alcohols.

Reduction of Nonyl Methyl Ketone.—Somewhat more than the theoretical amount of sodium (35 g. instead of 28 g.) is added to 100 g. of the ketone in 200 c.c. of absolute alcohol. It is necessary to cool the mixture at first, but later on the reaction must be completed by heating on a steam-bath. The product of the reaction is decomposed by the addition of water, the upper layer separated, washed with water, and steam distilled. The oil passing over into the distillate is removed by ether and distilled under reduced pressure; yield 63—76 g., b. p. 120°/14 mm. (Thoms and Mannich, *Ber.*, 1903, **36**, 2547).

This type of reduction has been applied successfully to many methyl alkyl ketones (Pickard and Kenyon, *J.*, 1911, **99**, 58; 1913, **103**, 1943), to many aryl alkyl ketones (Klages and Allendorff, *Ber.*, 1898, **31**, 1003; 1902, **35**, 2245), and to cyclic ketones.

Reduction by sodium in moist ether has given excellent results with a number of aliphatic ketones.

Reduction of Methyl n-*Butyl Ketone.*—Finely-divided sodium * (65 g.) is added gradually to a solution of 200 g. of the ketone in 1½ l. of ether to which have been added 300 c.c. of water. An efficient stirrer is required for this reduction. When the reaction is complete, the ethereal layer is separated, dried, and fractionated. The yield of methyl *n*-butyl carbinol is almost theoretical (Pickard and Kenyon, *J.*, 1914, **105**, 848; 1912, **101**, 629; compare J. Wislicenus, *Annalen*, 1883, **219**, 309).

While sodium is suited for the reduction of ketones it is not uniformly successful with aldehydes. Thus by the action of sodium amalgam on faintly acid solutions of butaldehyde and its immediate homologues only poor yields of the corresponding alcohols result (compare Lieben and Rossi, *Annalen*, 1871, **159**, 70; Lieben and Janeck, *ibid.*, 1877, **187**, 135; Rossi, *ibid.*, 1865, **133**, 180).

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* For preparation see p. 70.

A more successful procedure appears to be that employed for the reduction of heptaldehyde by Levene and Taylor (*J. Biol. Chem.*, 1918, **35**, 281). The aldehyde dissolved in a mixture of acetic acid and toluene is added to an emulsion of sodium in toluene. A yield of 70% of the theoretical is obtained.

Other methods which have been successfully employed include the use of aluminium amalgam (Weizmann and Garrard, *J.*, 1920, **117**, 324) and of zinc dust and acetic acid.

The reduction of the purely aromatic ketones to the corresponding carbinols can be effected smoothly in aqueous alcoholic solution using zinc dust and concentrated aqueous alkali or ammonia (A. Werner and Grob, *Ber.*, 1904, **37**, 2895; R. Meyer and Saul, *ibid.*, 1893, **26**, 1276; Elbs, *J. pr. Chem.*, 1886, [ii], **33**, 184).

The reduction of carbonyl compounds may lead not only to the corresponding alcohol, but also to the production of a glycol or pinacone according to the scheme

$$2(>\mathrm{CO}) + \mathrm{H}_2 \longrightarrow >\mathrm{C(OH)}\cdot\overset{|}{\underset{|}{\mathrm{C}}}(\mathrm{OH}).$$

The relative proportions of alcohol and glycol formed during reduction depend largely on the experimental conditions and also on the nature of the carbonyl compound. Thus acetone yields an appreciable amount of pinacone, $(\mathrm{CH}_3)_2\mathrm{C(OH)}\cdot\mathrm{C(OH)}(\mathrm{CH}_3)_2$, in addition to *iso*propyl alcohol. The yield of pinacone is increased at the expense of the alcohol by substituting aluminium or magnesium amalgams for sodium amalgam. The homologues of acetone behave similarly. Aliphatic aromatic ketones and aromatic ketones yield pinacones by suitable methods of reduction such as zinc and very dilute acid or the use of an alkaline solution (compare Böeseken and W. D. Cohen, *Proc. K. Akad. Wetensch. Amsterdam*, 1913, **16**, 91). Similar types can be obtained under suitable conditions by the reduction of aldehydes. Benzaldehyde yields a mixture of hydrobenzoin and *iso*hydrobenzoin on reduction with sodium in alcohol or with magnesium amalgam; piperonal behaves similarly (Fittig and Remsen, *Annalen*, 1871, **159**, 130; Fittig and Ammann, *ibid.*, 1873, **168**, 70). The aliphatic aldehydes do not show the same readiness to yield pinacone-like products on reduction, although by selecting the experimental conditions they may be obtained in small amount (Meunier, *Compt. rend.*, 1902, **134**, 473; Ciusa and Milani, *Atti R. Accad. Lincei*, 1913, [v], **22**, ii, 681).

Preparation of Pinacone.—Magnesium turnings (80 g.) and 800 c.c. of benzene, dried by distillation, are introduced into a 5-l. flask fitted with an efficient reflux condenser and a dropping funnel. A solution of 90 g. of mercuric chloride in 400 g. of dry acetone is added from the dropping funnel, at first cautiously and, when the reaction has set in, more quickly, so that interaction goes on as rapidly as possible without losing acetone through the condenser. As soon as the reaction caused by the addition of the mercuric chloride shows signs of subsiding, a mixture of 200 c.c. of benzene and 200 g. of acetone is added.

The mixture is finally heated in a water-bath for about 2 hours, when no further action is evident. By this time the flask is about three-quarters full of the magnesium salt of pinacone, which must be broken up in the flask and heated for a period of about 1 hour.

200 C.c. of water are now added to the contents of the flask, and the resulting mixture is heated for about 1 hour on the water-bath, then cooled to about 50° and filtered. The solid is returned to the flask and extracted with 500 c.c. of hot benzene for about 10 minutes to dissolve any remaining pinacone. The combined filtrate and extract are distilled to about one-third volume to remove acetone, and the remaining benzene solution is treated with 300 c.c. of water and cooled to 10—15°. Pinacone hydrate separates out and is collected on a Buchner funnel or centrifuged—yield of air-dried product, 325—375 g. It can be purified by crystallisation from an equal weight of boiling water (A. E. Holleman, *Rec. trav. chim.*, 1906, **25**, 206; R. Adams and E. W. Adams, *Organic Syntheses*, 1925, **5**, 87).

The reduction of aldehydes and ketones has been accomplished comparatively recently by a method which has some noticeable advantages over the older processes. Aldehydes are smoothly reduced to the corresponding alcohols by treating them in alcoholic solution with aluminium ethoxide. Disregarding at present the mechanism of the reaction, the effect can be represented by the following scheme :—

$$R\cdot CHO + R'\cdot CH_2OH \rightleftharpoons R\cdot CH_2\cdot OH + R'\cdot CHO$$

Obviously, if the reduction of the selected aldehyde is to approach completion, the experimental conditions should be chosen so that an excess of alcohol is used as solvent or that its oxidation product should be removed.

This process can be applied to ketones as well as to aldehydes, and has one marked advantage over methods employing the more usual reducing agents. It can be applied to unsaturated aldehydes and ketones and to halogen-substituted ketones and aldehydes without any reaction other than the reduction of the carbonyl group. Thus chloral, bromal, butyl chloral, trichloroacetophenone, and sorbic aldehyde are all converted by this method into the corresponding alcohols smoothly and in good yield. Nitrobenzaldehyde yields nitrobenzyl alcohol. Unsatisfactory results are obtained when the method is applied to hydroxyaldehydes such as aldol or to aminoaldehydes. Phenolic aldehydes are not reduced (Meerwein and R. Schmidt, *Annalen*, 1925, **444**, 221; Verley, *Bull. Soc. chim.*, 1925, [iv], 37, 537, 871; Ponndorff, *Z. angew. Chem.*, 1926, **39**, 138; Reichstein, Ammann, and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 261).

The following descriptions illustrate the experimental conditions for this type of reduction.

Preparation of Furfuryl Alcohol from Furfuraldehyde.—Freshly distilled furfuraldehyde (150 g.) is dissolved in 350 c.c. of alcohol and 45 g. of fused aluminium ethoxide * are added. The mixture becomes cloudy and the slight precipitate gradually increases on keeping. The mixture is kept at 25° till the furfuraldehyde has disappeared (test with aniline acetate). This requires about 5 days. The solvent is distilled off, the last traces being removed by heating in a bath at 120°. The residue is steam-distilled, the distillate saturated with potassium carbonate, and extracted with ether. After drying, the ether is removed by evaporation and the furfuryl alcohol distilled—yield 138 g., b. p. 172—173°.

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* For the preparation aluminium ethoxides see p. 71.

In a similar manner benzyl, anisyl, *p*-chlorobenzyl, and *p*-nitrobenzyl and cinnamyl alcohols have been prepared from the corresponding aldehydes, the yields being all over 80%.

A modification of this process consists in heating the alcoholic solution of the aldehyde in a stream of nitrogen, the conditions being arranged so that the acetaldehyde produced in the reaction is distilled over. These conditions have been used for the preparation of ββγ-trichlorobutyl alcohol from butyl chloral, and of tribromo- and trichloro-ethyl alcohols from bromal and chloral, respectively (Meerwein and Schmidt, *loc. cit.*).

Reduction of Sorbic Aldehyde to Sorbyl Alcohol.—A mixture of crude sorbic aldehyde (25 g.), 4—5 g. of aluminium *iso*propoxide, and 50 g. of anhydrous *iso*propyl alcohol is slowly distilled from an oil-bath, the volume in the flask being kept approximately constant by the continuous addition of further amounts of *iso*propyl alcohol. When no further amount of acetone distils over and the thermometer in the vapour stands at about 83°, the contents of the flask are concentrated by distillation to about 25 c.c. and then distilled in steam. The distillate from the last operation is extracted with ether and the ethereal solution dried and fractionated. The yield of sorbyl alcohol, $CH_3\cdot CH\colon CH\cdot CH\colon CH\cdot CH_2\cdot OH$, is about 19 g., b. p. 70—80°/12 mm. (Reichstein, Ammann, and Trivelli, *loc. cit.*).

Instead of using alcoholic solutions of aluminium alkoxides, alcoholic solutions of the alkoxyl magnesium chlorides may be employed. These substances are obtained by the action of the necessary amount of alcoholic hydrogen chloride or of alcoholic magnesium chloride on magnesium alkoxides, or more simply by heating magnesium with absolute alcohol containing sufficient hydrogen chloride to furnish the alkoxyl magnesium chloride, $(Alk)O\cdot MgCl$.

Reduction of Cinnamaldehyde to Cinnamyl Alcohol.—Ethoxymagnesium chloride is prepared by heating 2 g. of magnesium powder with 75 c.c. of absolute alcohol containing 3 g. of hydrogen chloride. The heating is continued till all the metal has reacted, magnesium ethoxy chloride partly separating out as a crystalline mass. A solution of 175 c.c. of absolute alcohol and 100 c.c. of cinnamic aldehyde is now added and the total mixture heated under a reflux maintained at 64° by vapour from boiling methyl alcohol. At the same time a stream of hydrogen or nitrogen is passed through the solution to carry away acetaldehyde formed in the reaction. After about 9 hours' heating, the reduction is complete. The solvent is distilled off and the residue acidified with sulphuric acid. The oil which separates is taken up in ether, dried, and fractionated. Yield of cinnamyl alcohol 75 g., b. p. 126—130°/7 mm., m. p. 27°.

Benzaldehyde, anisaldehyde, crotonaldehyde, nitrobenzaldehyde, citronellal are similarly reduced and in good yield (Meerwein and Schmidt, *Annalen*, 1925, **444**, 236).

For the reduction of ketones, wider variations of these processes may be employed. Instead of alcoholic solutions of aluminium alkoxides or magnesium alkoxy chlorides, the ketone may be reduced by heating with a sodium alkoxide dissolved in the appropriate alcohol (Verley, *loc. cit.*, p. 871; Ponndorff, *loc. cit.*, compare Diels and Rhodius, *Ber.*, 1909, **42**, 1072; Montagne, *Rec. trav. chim.*, 1922, **41**, 703). A few ketones may be reduced in toluene solution by heating with alcohol-free aluminium alkoxide (Meerwein and Schmidt, *loc. cit.*).

Preparation of Methyl Nonyl Carbinol.—A solution of sodium *iso*propoxide, prepared by dissolving 5 g. of sodium in 500 g. of dry *iso*propyl alcohol, is heated with 200 g. of methyl nonyl ketone so that a slow distillation takes place. After about 5 hours no more acetone distils over. The bulk of the *iso*propyl alcohol is then distilled off, the residue in the flask acidified and distilled in steam. Methyl nonyl carbinol is obtained from the distillate by extraction with ether, dried, and fractionated, yield 92% (Verley, *loc. cit.*).

Catalytic reduction of the aliphatic aldehydes and ketones to the corresponding alcohols has been effected smoothly and in good yield by the Sabatier–Senderens process of hydrogenation over reduced nickel at temperatures between 100° and 165° (Sabatier and Senderens, *Compt. rend.*, 1903, **137**, 301, 1025; Mailhe, *Bull. Soc. chim.*, 1914, [iv], **15**, 327). Aromatic ketones and mixed aliphatic aromatic ketones are reduced by this method at about 200° not to alcohols, but to the corresponding hydrocarbons.

Aldehydes and ketones in the liquid phase are not easily reduced by the Paal, Skita, or Willstätter methods of hydrogenation. By using specially prepared platinum oxide activated by iron salts as catalyst, the reduction of the carbonyl group to carbinol occurs readily (Voorhees and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 1397; Carothers and Adams, *ibid.*, 1923, **45**, 1071; 1924, **46**, 1675; 1925, **47**, 1047).

(2) *Reduction of* $>\mathrm{CO}$ *to* $>\mathrm{CH_2}$.—Although aromatic ketones may be reduced smoothly to diarylmethanes by treatment with sodium in hot ethyl or amyl alcoholic solutions (Klages and Allendorff, *Ber.*, 1898, **31**, 998), the method is not generally applicable to other types of ketones. For the conversion of aliphatic ketones to the corresponding hydrocarbons one general process depends on the intermediate formation of a dichloro-compound by the action of phosphorus pentachloride on the ketone, and subsequent reduction of the dichloro-compound with hydriodic acid and red phosphorus.

A method due to Clemmensen (*Ber.*, 1913, **46**, 1837; 1914, **47**, 51, 681) results in the reduction of aldehydes and ketones directly to the corresponding hydrocarbons. This is done by means of amalgamated zinc and hydrochloric acid, and has received a wide application. Not only are aliphatic and mixed aliphatic aromatic ketones reduced, but phenolic aldehydes and ketones yield homologues of phenol; thienyl alkyl ketones yield alkyl thiophenes (Steinkopf and Schubart, *Annalen*, 1921, **424**, 20); cyclic ketones such as α-hydrindone and α-ketotetrahydronaphthalene are reduced to hydrocarbons (Clemmensen, *Ber.*, 1914, **47**, 681; Krollpfeiffer and Schäfer, *ibid.*, 1923, **56**, 620). Keto*cyclo*paraffins containing very large rings are also reduced (Ruzicka, Brugger, Seidel, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 502; Ruzicka, Stoll, and Schinz, *ibid.*, p. 670; Ruzicka, Schinz, and Seidel, *ibid.*, 1927, **10**, 695; Ruzicka, Stoll, Huyser, and Boekenoogen, *ibid.*, 1930, **13**, 1152). More recently this process has been used in the synthesis of alkyl tetrahydro-naphthalenes and -phenanthrenes (Harvey, Heilbron, and D. G. Wilkinson, *J.*, 1930, 423; Heilbron and D. G. Wilkinson, *ibid.*, p. 2537; R. D. Haworth, Letsky, and Mavin, *ibid.*, 1932, 1784; R. D. Haworth and Bolam, *ibid.*, p. 2248).

The application of the method to other types of keto-compounds is not uniformly successful. Thus, while the aroyl fatty acids smoothly yield aryl-substituted fatty acids (Borsche, *Ber.*, 1919, **52**, 2077), acetoacetic ester and lævulic ester give only poor yields of the corresponding fatty esters (Steinkopf and Wolfram, *Annalen*, 1923, **430**, 113).

The technique of Clemmensen's reduction is illustrated by the following examples.

Preparation of Ethylbenzene from Acetophenone.—The amalgamated zinc is prepared by covering 400 g. of granulated zinc with 800 c.c. of 5% aqueous solution of mercuric chloride. After standing for 1 hour, the solution is poured off and 100 g. of acetophenone are added to the amalgamated zinc. Sufficient diluted hydrochloric acid (1 part conc. hydrochloric acid to 2 parts of water) is added to cover the zinc, and the mixture is heated under reflux for about 6 hours, small amounts of acid being added frequently. The upper oily layer consists principally of ethylbenzene, and is removed from the reaction mixture by distillation. Yield about 70%.

This method of reduction has been applied successfully to ethyl phenyl ketone, propyl phenyl ketone, methyl benzyl ketone, methyl phenylethyl ketone, and methyl α-naphthyl ketone. Benzaldehyde under similar conditions yields toluene in about 40% yield (Clemmensen, *Ber.*, 1913, **46**, 1840). *p*-Chloro-*n*-butylbenzene has also been prepared by this process from *p*-chlorobutyrophenone (Morgan and Hickinbottom, *J.*, 1921, **119**, 1887).

The alkyl ethers of the phenolic ketones can also be reduced smoothly by this method (T. B. Johnson and Hodge, *J. Amer. Chem. Soc.*, 1913, **35**, 1016; Majima and Nakamura, *Ber.*, 1913, **46**, 4090).

Smaller or greater amounts of the corresponding unsaturated hydrocarbons are formed in these reductions, an insufficiency of the reducing agent favouring the production of the unsaturated hydrocarbon. Replacement of aqueous hydrochloric acid by alcoholic solutions unfavourably affects the yield of saturated hydrocarbon, for the product then contains serious amounts of polymerised unsaturated hydrocarbons (Morgan and Hickinbottom, *loc. cit.*; Steinkopf and Wolfram, *loc. cit.*).

Reduction of Methyl n-*Nonyl Ketone to* n-*Undecane.*—A mixture of 300 g. of amalgamated zinc, 50 g. of methyl *n*-nonyl ketone, and 300 c.c. of diluted hydrochloric acid (equal vols. of conc. acid and water) are heated together for 24 hours with the frequent addition of concentrated acid. The colourless upper layer is separated at the end of the reaction, washed with water, and dried. Yield 40 g., b. p. 193—195°.

Stearone, methyl heptadecyl ketone, and œnanthaldehyde are reduced to the corresponding hydrocarbons under precisely similar conditions.

Reduction of p-*Hydroxyacetophenone to* p-*Ethylphenol.*—Amalgamated zinc

(100 g.), *p*-hydroxyacetophenone (50 g.), and 500 c.c. of diluted hydrochloric acid (1 vol. conc. acid to 2 vols. of water) are heated together under reflux till a vigorous evolution of hydrogen commences. The ketone rapidly goes into solution, and soon oily drops commence to separate. Small amounts of concentrated hydrochloric acid are added at intervals during 1 hour. Steam distillation of the reaction product drives over the ethyl phenol which is isolated from the distillate by saturating with potassium carbonate and extracting with ether. Concentration of the dried ethereal extract yields the phenol which solidifies on keeping. Yield 22 g., b. p. 217°, m. p. 45—46°.

Ketones derived from *o*-cresol, resorcinol, quinol, catechol, and pyrogallol are similarly reduced to alkyl-substituted phenols.

Preparation of o-*Cresol from Salicylaldehyde.*—150 G. of amalgamated zinc and 200 c.c. of concentrated hydrochloric acid are warmed together under reflux till an evolution of hydrogen commences. Salicylaldehyde is then added drop by drop through the condenser, and small amounts of concentrated hydrochloric acid are added at intervals. When all the aldehyde (25 g.) has been added the mixture is heated under reflux for 1 hour with the occasional addition of concentrated hydrochloric acid. The product is isolated by distillation in steam, saturating the distillate with salt, and extracting the cresol from it by light petroleum. After drying and fractionating, pure *o*-cresol, b. p. 189°, is obtained—yield 15 g.

m- and *p*-Cresols and 2 : 4-dihydroxytoluene have been obtained from the corresponding hydroxy aldehydes by a similar process (Clemmensen, *Ber.*, 1914, **47**, 51).

An interesting type of reduction of the $>CO$ group to $>CH_2$ consists in heating the semicarbazone or hydrazone of the carbonyl compound with sodium ethoxide to about 170—180° (Wolff, *Annalen*, 1912, **394**, 90). The method has been applied successfully to acetophenone, *p*-aminoacetophenone, benzophenone, lævulic acid, methyl butyl ketone, and to aldehydes such as anisaldehyde, furfural, and vanillin.

A somewhat similar process has been developed by Staudinger and Kupfer (*Ber.*, 1911, **44**, 2206), and consists in heating the aldehyde or ketone with an excess of hydrazine at about 200°.

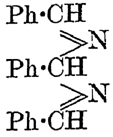
(c) *Reaction of the Carbonyl Group with Ammonia and Compounds containing the* $R{\cdot}NH_2$ *Grouping.*

1. *Amines and Ammonia.*—The primary product of the reaction of a primary amine or ammonia with an aldehyde can be looked upon as the addition compound $R{\cdot}CH(OH){\cdot}NHR$, which may lose the elements of water to give an azomethine or may undergo further condensation.

Only comparatively few amines and aldehydes yield the simple addition compound. Formaldehyde is stated to react with methylamine or ethylamine to give hydroxyamines of the general formula $CH_2(OH){\cdot}NHR$ (L. Henry, *Bull. Acad. roy. Belg.*, 1895, [iii], **28**, 359). This reaction has an interesting application in syntheses (G. M. and R. Robinson, *J.*, 1923, **123**, 532).

Concentrated aqueous ammonia acting on acetaldehyde or dry ammonia on an ethereal solution of acetaldehyde yields the well-known acetaldehyde ammonia. The analytical figures correspond with the formula $CH_3{\cdot}CH(OH){\cdot}NH_2$, but the investigations of Delépine (*Bull. Soc. chim.*, 1898, [iii], **19**, 15; 1899, [iii], **21**, 58) and of Aschan and Vaskio (*Ber.*, 1915, **48**, 874) indicate that the product is more complex. Its molecular weight in water corresponds with the formula $3[CH_3{\cdot}CH(OH){\cdot}NH_2]$. The substance loses water over sulphuric acid, but can be rehydrated to the original aldehyde ammonia. No general agreement on its structure has yet been reached. A similar type of compound is obtained from chloral.

Treatment of benzaldehyde with concentrated ammonia forms hydrobenzamide,



$$\begin{array}{l} Ph{\cdot}CH \\ \qquad >N \\ Ph{\cdot}CH \\ \qquad >N \\ Ph{\cdot}CH \end{array}$$

Many other aromatic aldehydes behave in the same way. It appears that the formation of this type of compound—at least from benzaldehyde and anisaldehyde—is preceded by the production of an unstable additive compound of the general formula $(R{\cdot}CHO)_2,NH_3$ (Francis, *Ber.*, 1909, **42**, 2216).

Although the usual behaviour of benzaldehyde and its homologues with primary aromatic amines is to give azomethines, some nitrobenzaldehydes, particularly 2 : 4 : 6-trinitrobenzaldehyde, yield additive compounds of the general type $R{\cdot}CHO,NH_2R'$, which furnish the corresponding azomethine $R{\cdot}CH{:}NR'$ on warming alone or with acetic acid (Lowy and Balz, *J. Amer. Chem. Soc.*, 1921, **43**, 344). It should be noted that the hydrochloride of the additive compound $PhNH{\cdot}CH(OH){\cdot}Ph$ is formed by the action of benzaldehyde on an aqueous solution of aniline hydrochloride. The sulphite is obtained by interaction of aniline with benzaldehyde bisulphite (Dimroth and Zoeppritz, *Ber.*,1902, **35**, 988; Bucherer and Schwalbe, *ibid.*, 1906, **39**, 2810).

The commonest type of reaction between a primary amine and an aldehyde results in the formation of an azomethine :—

$$R{\cdot}CHO + H_2N{\cdot}R' \longrightarrow R{\cdot}CH{:}NR' + H_2O$$

It had been observed in the case of aniline and benzaldehyde as early as 1850 by Laurent and Gerhardt (*Annalen*, 1850, **76**, 304). Later Schiff (*ibid.*, *Spl.*, 1864, 3, 343) found that many aromatic and aliphatic aldehydes condensed with aniline in a similar way. The formation of Schiff's bases or azomethines succeeds best with aromatic aldehydes and primary aromatic amines, for the products show comparatively little tendency to polymerise. As many of them are crystalline, they are frequently used for the characterisation of aldehydes and primary amines. The condensation is effected by warming the components together in approximately equimolecular proportions, either diluted with a suitable solvent such as alcohol or acetic acid or without any diluent (compare Lowy and Downey, *J. Amer. Chem. Soc.*, 1921, **43**, 346; Lowy and C. S. King, *ibid.*, p. 626).

The azomethines derived from the lower aliphatic aldehydes and primary aromatic amines are less stable than those from the aromatic aldehydes. Thus acetaldehyde and aniline yield, under suitable conditions, the compound $CH_3{\cdot}CH{:}NHPh$, which rapidly polymerises. With excess of aniline the compound $CH_3{\cdot}CH(NHPh)_2$ is formed (v. Miller, Plöchl, and Eckstein, *Ber.*, 1892, **25**, 2030; Eibner, *ibid.*, 1897, **30**, 1446; *Annalen*, 1903, **328**, 121).

The tendency for azomethines to polymerise or to undergo other reactions is most marked with those derived from formaldehyde. With ammonia, formaldehyde yields hexamethylenetetramine, $(CH_2)_6N_4$, the formation of which has been represented as proceeding through the intermediate compound $(CH_2{:}NH)_3$ (Duden and Scharff, *Annalen*, 1895, **288**, 218). Condensation of formaldehyde with aromatic amines results in the formation of Schiff's bases. These are comparatively unstable, polymerising or combining with further amounts of the reactants. The reaction of formaldehyde with *p*-toluidine illustrates this condensation. The azomethine, $CH_2{:}N{\cdot}C_6H_4{\cdot}CH_3$, readily polymerises to a di- or tri-meric form. On the other hand, it may combine with an excess of *p*-toluidine to give $CH_2(NH{\cdot}C_6H_4CH_3)_2$, which in turn can react with a further amount of formaldehyde (Ingold and Piggott, *J.*, 1923, **123**, 2745; J. G. Miller and E. C. Wagner, *J. Amer. Chem. Soc.*, 1932, **54**, 3698). Aniline and formaldehyde give methylene aniline, $CH_2{:}NPh$, which readily polymerises to anhydroformaldehyde aniline, $(CH_2{:}NPh)_3$. It can further combine with aniline to yield $CH_2(NHPh)_2$.

The reaction between ketones and amines takes place much less readily than with aldehydes. Thus benzophenone can be heated with aniline at 160° without any reaction taking place. The preparation of anils from aromatic ketones and mixed aromatic aliphatic ketones requires the presence of a catalyst. Zinc chloride appears to be very suitable for this purpose (Reddelien, *Annalen*, 1912, **388**, 165).

Preparation of Acetophenone Anisil.—A mixture of acetophenone (10 g.) and *p*-anisidine (10 g.) is heated to 165°, when 0·5 g. of anisidine zincichloride is added. A vigorous evolution of vapour occurs, and after 20 minutes the mixture is cooled, dissolved in chloroform, and filtered. Fractionation of the filtrate under reduced pressure yields the pure acetophenone anisil, b. p. 225°/28 mm., which solidifies on cooling—yield 14 g.

It is possible to obtain the ketimines of the aromatic ketones by passing the vapour of the ketone mixed with ammonia over thorium oxide at 300—400° (Mignonac, *Compt. rend.*, 1919, **169**, 237). The aliphatic ketimines cannot be prepared by this method.

2. *Reaction with Hydrazine and its Derivatives.*—Hydrazine condenses with the carbonyl group of aldehydes and ketones to give hydrazones of the general formula $>C{:}N{\cdot}NH_2$, which can react with a further molecule of the carbonyl compound to give azines, $>C{:}N{\cdot}N{:}C<$. For the preparation of these compounds hydrazine hydrate may be used. It is, however, usually more convenient to use an aqueous solution of some salt such as the sulphate to which

has been added the requisite amount of alkali or alkali carbonate or an excess of sodium acetate (compare G. M. and R. Robinson, *J.*, 1918, **113**, 644).

The substituted hydrazines $RNH{\cdot}NH_2$ and $RR'N{\cdot}NH_2$ (where R and R′ are alkyl and aryl groups) react similarly to yield hydrazines. Phenylhydrazine is the most readily accessible substituted hydrazine, and it is extensively used for the recognition and characterisation of compounds containing the carbonyl group. Phenylhydrazones are generally prepared by mixing the aldehyde or ketone with phenylhydrazine, usually diluted with a suitable solvent. With most aldehydes and many ketones the condensation is complete at room temperature, but it is usual to complete the reaction by warming gently. As solvents, ether and alcohol have been used, but 30—50% acetic acid is most convenient. A large number of other arylhydrazines have been employed, and many have special advantages which recommend their employment. Thus *p*-nitrophenylhydrazine and 2 : 4-dinitrophenylhydrazine yield crystalline hydrazones with aliphatic aldehydes and ketones, most of which yield oily products with phenylhydrazine. The nitrophenylhydrazines find therefore extensive application for the characterisation of such aldehydes and ketones.

Preparation of 2 : 4-Dinitrophenylhydrazones.—The following general directions are based on those given by Allen (*J. Amer. Chem. Soc.*, 1930, **52**, 2957) and by Brady (*J.*, 1931, 757).

The reagent is a saturated solution of 2 : 4-dinitrophenylhydrazine in alcohol (about 1% concentration) containing 1% of hydrochloric acid. About 5 c.c. of this solution are added to a few drops of a liquid carbonyl compound or a few centigrams of solid carbonyl compound dissolved in alcohol. Separation of a crystalline hydrazone may commence almost immediately after mixing. If after keeping at room temperature for a short time there is no precipitate, the mixture may be warmed gently and kept overnight in a corked vessel.

The addition of a small amount of concentrated hydrochloric acid may accelerate the formation of the hydrazone.

Other hydrazines which have been used are *o*-, *m*-, and *p*-tolylhydrazine, *p*-bromophenylhydrazine, αα-methylphenylhydrazine, αα-benzylphenylhydrazine, αα-diphenylhydrazine, and β-naphthylhydrazine. Most of these find special application for the characterisation of reducing sugars. The use of *m*-hydrazinobenzoic acid has been recommended for the separation of aldehydes and ketones from other substances (Willstätter, Schupple, and Mayer, *Annalen*, 1919, **418**, 127).

Hydrazine derivatives other than the aryl- and arylalkylhydrazines are frequently employed for the characterisation and recognition of carbonyl compounds. Of these, semicarbazide, $NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$, gives crystalline condensation products with most aldehydes and ketones and is extensively used. Other reagents less commonly employed are thiosemicarbazide, $NH_2{\cdot}CS{\cdot}NH{\cdot}NH_2$; benzoylhydrazine, $PhCO{\cdot}NH{\cdot}NH_2$, and its nitro-substituted derivatives; semioxamazide, $NH_2 \cdot CO \cdot CO \cdot NH \cdot NH_2$; and aminoguanidine, $NH_2 \cdot C(:NH) \cdot NH \cdot NH_2$.

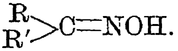
The commercial hydrochloride is the most accessible form of semicarbazide for the preparation of semicarbazones. A concentrated aqueous solution of it is added to a solution of the ketone or aldehyde in alcohol or dilute acetic acid. The separation of the semicarbazone may occur almost immediately, and is completed by the addition of solid potassium acetate. Some semicarbazones require several days after the addition of the acetate for their formation. If the aldehyde or ketone is soluble in water, it is unnecessary to use organic solvents. Hopper (*J. Roy. Tech. College, Glasgow,* 1929, **2**, [i], 52) describes a method of general application for this preparation using pyridine as a solvent.

The benzoyl- and nitrobenzoyl-hydrazines have been recommended for the characterisation of carbonyl compounds. The resulting hydrazones are generally sparingly soluble crystalline solids (Curtius and co-workers, *J. pr. Chem.*, 1894, [ii], **50**, 275, 295; 1895, [ii], **51**, 165, 353).

Semioxamazide has been used for the characterisation of aldehydes when the semicarbazones are not satisfactory (Kerp and Unger, *Ber.*, 1897, **30**, 585; Radcliffe, *Perf. and Essential Oil Record,* **1919**, **10**, 39). The reaction appears to be a general one for aldehydes; for ketones special precautions are necessary. Suitable experimental conditions with this object are described by Wilson and Pickering (*J.*, 1923, **123**, 394; 1924, **125**, 1152).

Thiosemicarbazide yields thiosemicarbazones by reaction with aldehydes and ketones, which form sparingly soluble silver, mercury, or copper salts. The preparation of these salts can be used for the analysis of thiosemicarbazones, or for the separation of carbonyl compounds from mixtures containing other substances, since these salts regenerate the original aldehyde or ketone by the action of mineral acids (Neuberg and Neumann, *Ber.*, 1902, **35**, 2049; Baird, Burns, and Wilson, *J.*, 1927, 2527; Bose and Chaudhury, *J. Indian Chem. Soc.*, 1927, **4**, 84).

The condensation products of aminoguanidine with aldehydes and ketones are characterised by their comparatively strong basicity and yield, in general, sparingly soluble picrates and nitrates (Baeyer, *Ber.*, 1894, **27**, 1919; Thiele and Dralle, *Annalen*, 1898, **302**, 278; Thiele and Bihan, *ibid.*, p. 302).

3. *Reaction with Hydroxylamine.*—Aldehydes and ketones react with hydroxylamine to eliminate the elements of water and to yield oximes of the general formula  $\genfrac{}{}{0pt}{}{R}{R'}\!>\!C{=}NOH$.

A general method of preparation consists in mixing the aldehyde with the necessary amount of hydroxylamine hydrochloride dissolved in water to which a slight excess of sodium carbonate or bicarbonate ($1\frac{1}{4}$—$1\frac{1}{2}$ times the necessary amount) has been added. Oximation is completed by keeping at room temperature. With aldehydes which are insoluble in water, alcohol may be used as a solvent.

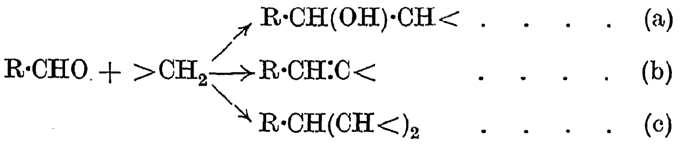
Instead of sodium carbonate, 2 molecular proportions of sodium hydroxide in aqueous solution may be used, but under these conditions the oxime must be liberated by saturating the solution with carbon dioxide.

Ketoximes may be prepared by a similar method, but as the reaction generally proceeds less readily, it must usually be completed by warming. The hydroxylamine salt is heated with an aqueous or alcoholic solution of the ketone after adding potassium acetate or the exact amount of caustic soda to liberate the hydroxylamine.

(4) *Effect of Configuration on the Reaction of Aldehydes and Ketones with Hydrazines and Hydroxylamine.*—The relative ease with which aldehydes and ketones react with hydroxylamine and substituted hydrazines has been examined by several investigators. It appears that the accumulation of groups adjacent to the carbonyl group retards the reaction, and may even prevent it. Thus methyl *iso*propyl ketone is less reactive than acetone, while in the aromatic series the presence of groups in the *ortho* position seriously retards the formation of oximes and phenylhydrazones. Examples and references to the literature are given by A. W. Stewart (*Stereochemistry*, 1907, pp. 416—426). There is evidence to show that the reactivity of aldehydes and ketones does not entirely depend on spatial considerations. The reagent itself also appears to have quite a definite influence (Michael, *J. Amer. Chem. Soc.*, 1919, **41**, 393).

(d) *Reaction of the Carbonyl Group with the Methylene Group.*

Aldehydes in general condense with suitably activated $>CH_2$ groupings to give compounds which belong to one of the three following types :



$$\begin{array}{lll} & \nearrow R\cdot CH(OH)\cdot CH< \quad . \quad . \quad . \quad . & (a) \\ R\cdot CHO + >CH_2 & \longrightarrow R\cdot CH{:}C< \quad . \quad . \quad . \quad . & (b) \\ & \searrow R\cdot CH(CH<)_2 \quad . \quad . \quad . \quad . & (c) \end{array}$$

The reaction occurs between the carbonyl and the methylene groupings. It occurs also with the carbonyl group of ketones, although not to the same extent. For this type of reaction to take place, the methylene group requires the activating influence of an adjacent $>CO$, $-CN$ or $-NO_2$ grouping. A heterocyclic, or an aromatic group, or a conjugated system have the same effect. These classifications include simple acids and their esters, ketones, nitroparaffins, nitriles, 1 : 3-diketones such as acetyl acetone and benzoyl acetone, β-ketonic esters as acetoacetic ester, α-cyano-acids as cyanoacetic ester, α-methylpyridine, fluorene, quinaldine, lepidine, *cyclo*pentadiene, indene. This type of reaction has therefore a wide application and is of very considerable importance. It includes such well-known reactions as the Perkin, Knoevenagel, and Doebner methods of preparing unsaturated acids, the aldol reaction and the crotonaldehyde condensation.

The experimental conditions for the reaction are very diverse, and although it is possible to classify them according to the type of condensing agent used, it seems more convenient in the following account to consider these reactions according to the type of reactants concerned.

(1) *Reaction of the Carbonyl Group with Aldehydes and Ketones.*—The simplest type of reaction is that exemplified by the aldol reaction, two molecules of a suitable aldehyde reacting under the influence of a suitable catalyst to give a β-hydroxyaldehyde according to the scheme

$$R{\cdot}CH_2{\cdot}CHO + R{\cdot}CH_2{\cdot}CHO \longrightarrow R{\cdot}CH_2{\cdot}CH(OH){\cdot}CHR{\cdot}CHO$$

where R is an alkyl group. There is evidence that, in this reaction, an equilibrium between the aldehyde and the aldol is set up (Usherwood, *J.*, 1923, **123**, 1717).

A large variety of catalysts have been used to bring it about. Wurtz (*J. pr. Chem.*, 1872, [ii], **5**, 457), who first prepared aldol, used hydrochloric acid (compare Kolbe, *J. pr. Chem.*, 1872, [ii], **5**, 465). More suitable catalysts are potassium carbonate or potassium cyanide, sodium acetate, dilute sodium hydroxide solution, or sodium sulphite.

Preparation of Aldol.—Freshly prepared acetaldehyde (from paraldehyde, see p. 147) (100 g.) is added to 200 g. of ice and water and the resulting solution cooled to − 12° and stirred mechanically. A solution of 2·5 g. of potassium cyanide in 100 g. of water is now added slowly so that the temperature never rises above − 8°. When all the cyanide has been added the solution is kept in the freezing mixture for 2 hours and then in an ice-chest for about 30 hours more. The solution has then a pale yellow colour and has become more viscous. The aldol is isolated from it by four extractions with ether after saturating the aqueous solution with salt.

Evaporation of the ethereal solution leaves a thick oily residue, which on distillation under reduced pressure yields 40—50 g. of aldol, b. p. 80—90°/20 mm. (Claisen, *Annalen*, 1899, **306**, 322).

The homologues of acetaldehyde react similarly, provided that the grouping $-CH_2{\cdot}CHO$ is present. The behaviour of aldehydes not possessing this grouping is discussed later (p. 160).

Under more drastic conditions, the reaction goes further, either to furnish an unsaturated aldehyde by the loss of water or the aldol may undergo a further condensation (Lieben, *Monatsh.*, 1901, **22**, 289; Neustädter, *ibid.*, 1906, **27**, 903; Raper, *J.*, 1907, **91**, 1831).

The formation of the unsaturated aldehyde is favoured by effecting the condensation in presence of zinc chloride. In its presence two different aldehydes may similarly undergo condensation to give unsaturated aldehydes. Thus acetaldehyde condenses with *n*-heptaldehyde to give α-ethylidene *n*-heptaldehyde,

$$CH_3{\cdot}(CH_2)_4{\cdot}C(CHO){:}CH{\cdot}CH_3$$

(Zaar, *Ber. Schimmel*, 1929, 309). Other condensing agents may also be employed.

Preparation of α-Phenylcinnamaldehyde, $Ph{\cdot}CH{:}C(Ph){\cdot}CHO$.—A solution of 20 c.c. of 5% methyl alcoholic solution of sodium methoxide is added to a cooled mixture of benzaldehyde (53 g.) and phenylacetaldehyde (60 g.). The mixture is neutralised with acetic acid after keeping overnight and then fractionated. Redistillation of the fraction b. p. 150—210°/18 mm. gives 20—30 g. of a straw-coloured oil, b. p. 196—201°/16 mm., which solidifies almost completely on cooling. Crystallisation of the aldehyde from alcohol gives an approximately pure product, m. p. 94—95° (Burton, *J.*, 1932, 748; Meerwein and Dott, *J. pr. Chem.*, 1918, [ii], **97**, 281).

A similar reaction occurs between aliphatic aldehydes and ketones. Thus acetaldehyde or butaldehyde reacts with acetone to give a hydroxy-ketone (I), which under suitable conditions loses the elements of water to form an unsaturated ketone (II).

$$\mathrm{R{\cdot}CHO + CH_3{\cdot}CO{\cdot}CH_3 \longrightarrow \underset{(I.)}{R{\cdot}CH(OH){\cdot}CH_2CO{\cdot}CH_3} \longrightarrow \underset{(II.)}{R{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_3}}$$

The condensing agents employed in these reactions are alkali or dilute aqueous alkali cyanides. Occasionally acids are used (J. G. Schmidt, *Ber.*, 1881, **14**, 1459; Claisen, *ibid.*, p. 2468; 1892, **25**, 3164).

The following examples illustrate the experimental conditions for this reaction.

Reaction of n-*Butaldehyde with Acetone.* (a) *Formation of Heptane-δ-ol-β-one* (formula I, R = C_3H_7).—A solution of 72 g. of *n*-butaldehyde in 58 g. of acetone is added during a period of 3 hours to a mechanically stirred mixture of 116 g. of acetone and 20 g. of sodium hydroxide in 40 c.c. of water maintained at 5—10°. The mixture is stirred for a further period of an hour after the addition of all the aldehyde. The aqueous layer is then separated, extracted with ether, and the ethereal solution added to the oil. The combined product is neutralised with dilute acetic acid, and washed with bicarbonate solution and water. It is then dried and fractionated, after removing the solvent and acetone under reduced pressure at the ordinary temperature. The hydroxy-ketone is collected at 92—95°/12 mm. as a pale yellow oil with a faint odour.

If the reaction is allowed to proceed without cooling, the product contains a comparatively large amount of the unsaturated ketone.

(b) *Formation of* cis-n-*Butylidene Acetone* (formula II, R = C_3H_7).—*n*-Butaldehyde (178 c.c.) is added slowly to a mixture of acetone (145 c.c.) and 320 c.c. of 15% aqueous sodium hydroxide solution. The initially vigorous reaction is allowed to proceed under reflux and is finished by shaking mechanically for 2 days. The oil is separated and the aqueous layer extracted with ether. The combined oil and extracts are washed with water and dried with calcium chloride. Fractionation under reduced pressure gives the crude ketone, b. p. 70°/12 mm. The product still contains some water, which is best removed by adding an equal volume of benzene and distilling it off through a fractionating column. The residue gives, on distillation under reduced pressure, the pure ketone, b. p. 67—70°/12 mm. (Eccot and Linstead, *J.*, 1930, 911).

Reaction of n-*Butaldehyde with Methyl Ethyl Ketone.*—*n*-Butaldehyde (72 g.) is added drop by drop to a well-stirred mixture of 220 g. of methyl ethyl ketone and 50 c.c. of *N*-alcoholic potash. Slightly more than the theoretical amount of tartaric acid is added and the precipitate of potassium hydrogen tartrate collected. As much as possible of the unchanged ketone is removed by distillation from a water-bath and the residue fractionated under reduced pressure. The principal fractions are collected at about 85°/20 mm. and 105—112°/16 mm. A further fractionation gives pure δ-hydroxy-γ-methyl-β-heptanone, b. p. 110°/16 mm.—yield 60 g.

The lower-boiling fraction is the unsaturated ketone. It can very conveniently be obtained from the hydroxy-ketone by the following method.

Iodine (1 g.) is added to 144 g. of the hydroxy-ketone and the mixture slowly distilled. Water commences to separate almost immediately, and distils over, carrying with it some of the ketone. The main fraction of the unsaturated ketone is collected at 170—175° and is purified by distillation under reduced pressure (Powell, *J. Amer. Chem. Soc.*, 1924, **46**, 2514).

Preparation of Benzalacetone.—Freshly distilled benzaldehyde (42 g.), acetone (80 c.c.), and 40 c.c. of water are mixed in a beaker flask and 10 c.c. of a 10% solution of sodium hydroxide added gradually. The mixture is stirred mechanically and the temperature is maintained between 25° and 31° by regulating the rate of addition of the alkali and by providing an external cooling bath. When all the alkali has been added, the stirring is continued for a period of 2 hours, and then dilute hydrochloric acid is added till the mixture is neutral to litmus. The two layers are separated and the lower extracted once with benzene. The oil obtained in the condensation is added to the benzene extract, the combined solution washed with water and fractionated under reduced pressure. Benzalacetone is collected at 133—143°/16 mm. as an almost colourless oil which solidifies on nucleation. It may be purified by a further distillation—yield 37—45 g. (Drake and Allen, jr., *Organic Syntheses*, 1923, **3**, 17).

Preparation of Benzalacetophenone.—A solution of 21 g. of sodium hydroxide in 200 c.c. of water and 100 c.c. of alcohol in a $\frac{1}{2}$-litre beaker flask is cooled by an external bath of ice and stirred mechanically. Acetophenone (52 g.) is added to the alkaline solution and then 46 g. of benzaldehyde. The temperature is maintained between 15° and 30°.

After some time, the mixture becomes so viscous that stirring must be discontinued. The mixture is then kept in an ice-box overnight. The ice-cold mixture is filtered and washed with water till neutral to litmus, and then with a small amount of ice-cold alcohol. The yield of the crude product is about 88 g. It can be purified by crystallisation from alcohol, m. p. 55—57° (Kohler and Chadwell, *Organic Syntheses*, 1922, **2**, 1).

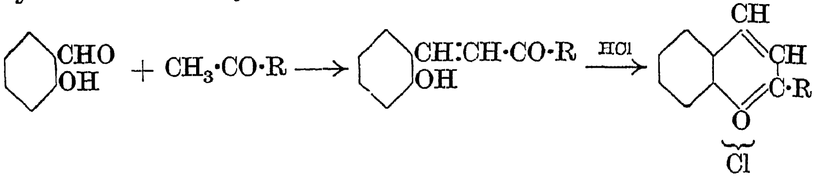
Preparation of Cinnamylpyruvic Acid.—A mixture of cinnamaldehyde (20 g.) and pyruvic acid (15 g.) (both freshly distilled under reduced pressure) is added to a well-cooled and efficiently stirred solution of 9 g. of sodium hydroxide in 120 c.c. of 50% alcohol. The first few drops produce a fine suspension which gives place to a yellow crystalline precipitate. This gradually increases in amount as further amounts of the reactants are added. The addition requires about $\frac{3}{4}$ hour, and after all the acid has been added the reaction mixture is stirred for 2 or 3 hours at room temperature. The pasty light yellow mass is collected, thoroughly drained and washed with alcohol (96%). It is then dried under reduced pressure over calcium chloride—yield 21 g. This is the sodium salt of cinnamylidene pyruvic acid, $Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO{\cdot}CO_2H$, and is purified by crystallisation from eight times its weight of 50% alcohol (Friedmann and Mai, *Helv. Chim. Acta*, 1931, **14**, 1213).

The condensation of *o*-nitrobenzaldehyde and its substitution products with acetone is of importance in that it supplies a method for the preparation of indigo and its substituted products. The normal condensation is brought about by the action of the alkali salts of weak acids such as sodium sulphite or trisodium phosphate. If alkali is used, the reaction yields indigo (compare F. Sachs and Kempf, *Ber.*, 1903, **36**, 3302).

Cyclic ketones condense with aldehydes in the same way as open-chain ketones.

Preparation of 2-Hydroxy-2-benzylidene-1-hydrindone.—Hydrindone and salicylaldehyde (10 g. each) are heated together with a solution of 4 g. of caustic potash in 50 c.c. of methyl alcohol for 20 minutes. The product is acidified with acetic acid, diluted with water, and the bright canary-yellow precipitate collected, washed with water, and crystallised from alcohol. It separates from boiling alcohol in slender, canary-yellow needles, m. p. 206° (W. H. Perkin, jr., and Robinson, *J.*, 1907, **91**, 1087).

The condensation of ketones with salicylaldehyde and other *o*-hydroxy-aromatic aldehydes is of considerable importance in that the unsaturated ketone produced in the reaction can undergo ring formation under the influence of hydrogen chloride to yield a benzopyrylium salt. This type of reaction has been extensively used by Robinson and his co-workers for the synthesis of anthocyanins and anthocyanidins.

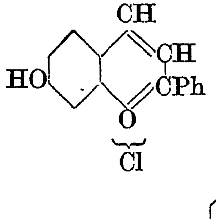


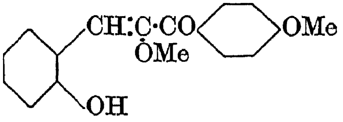
Preparation of 7-Hydroxy-2-phenyl-benzopyrylium Chloride (III).—Acetophenone (5 g.) and β-resorcylaldehyde (5 g.) are dissolved in 25 c.c. of glacial acetic acid and a slow stream of hydrogen chloride is passed into the cooled solution. The liquid first becomes yellow, then red, and after a few hours orange-yellow crystals of the pyrylium salt separate. After standing overnight the crystals are collected, washed with acetic acid, and recrystallised from dilute hydrochloric acid (Perkin, Robinson, and M. R. Turner, *J.*, 1908, **103**, 1098).

Preparation of 3 : 4′-Dimethoxy-2-phenylbenzopyrylium Ferrichloride (V).—Salicylaldehyde (2·8 g.) and ω : 4-dimethoxyacetophenone (4 g.) are boiled together for 2 hours in methyl alcohol (100 c.c.) containing 1·5 g. of potassium hydroxide. The reaction mixture is acidified with acetic acid after cooling and diluting. The crude ketone (IV)—4′-methoxy-2-hydroxy-β-methoxystyryl ketone—is purified by crystallisation from methyl alcohol, m. p. 160°.

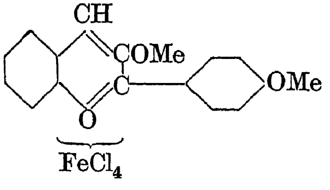
Conversion of the unsaturated ketone into the benzopyrylium salt is effected by passing a slow stream of hydrogen chloride into its solution (3 g.) in 100 c.c. of dry ether for 1 hour. A solution of ferric chloride in hydrochloric acid is then added, the solvent removed by cautious distillation, and the precipitate of the ferrichloride collected. It separates from glacial acetic acid in hair-fine orange-red needles (D. D. Pratt and Robinson, *J.*, 1923, **123**, 751).

(III.)





(IV.)



(V.)

For the application of these reactions to the syntheses of anthocyanins and anthocyanidins the following papers should be consulted: Pratt and Robinson, *J.*, 1924, **125**, 197; 1925, **127**, 170; Gatewood and Robinson, *ibid.*, 1926, 1959; A. Robertson and Robinson, *ibid.*, 1926, 1714, 1951; 1928, 1525; Nolan, Pratt, and Robinson, *ibid.*, 1926, 1968; Robertson, Robinson, and Sugiura, *ibid.*, 1928, 1533; Murakami and Robinson, *ibid.*, 1928, 1537; Bradley and Robinson, *ibid.*, 1928, 1566; Bradley, Robinson, and Schwarzenbach, *ibid.*, 1930, 793, 815; León, Robertson, Robinson, and Sheshadri, *ibid.*, 1931, 2672; León and Robinson, *ibid.*, 1932, 2223.

To the type of reactions considered in the foregoing section must be added the self-condensations of acetone, methyl ethyl ketone, *cyclo*hexanone, and other ketones.

Acetone in the presence of alkali under carefully controlled conditions undergoes a reaction quite analogous to the aldol condensation of acetaldehyde. Two molecules react according to the scheme to give diacetone alcohol (VI)

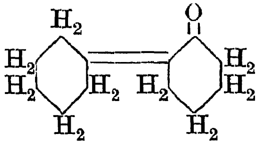
$$CH_3{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}CO{\cdot}CH_3 \longrightarrow (CH_3)_2C(OH){\cdot}CH_2{\cdot}CO{\cdot}CH_3 \quad \text{(VI.)}$$

(VI) suffers dehydration either by distillation with iodine, or, if the conditions of alkaline condensation of acetone are vigorous, to furnish mesityl oxide. This compound has long been known as a product of the action of quick-lime, hydrogen chloride, sodium alkoxides, etc., on acetone (Kane, *On a Series of Combinations from Pyroacetic Spirit*, Dublin, 1838; *J. pr. Chem.*, 1838, [i], **15**, 129; Fittig, *Annalen*, 1859, **110**, 32; Baeyer, *ibid.*, 1866, **140**, 301; Claisen, *ibid.*, 1876, **180**, 1). The condensation can be made to proceed further with the production of phorone $(CH_3)_2C{:}CH{\cdot}CO{\cdot}CH{:}C(CH_3)_2$, isophorone, xylitone $C_{12}H_{18}O$, and mesitylene (Kerp, *Annalen*, 1896, **290**, 137; Kerp and F. Müller, *ibid.*, 1897, **299**, 93; Knoevenagel, *ibid.*, 1897, **297**, 185; Crossley and Gilling, *J.*, 1909, **95**, 18).

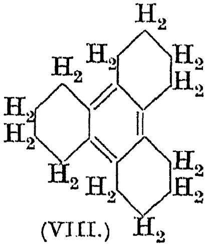
Methyl ethyl ketone and diethyl ketone can in the same way be induced to undergo similar reactions (Bodroux and Taboury, *Bull. Soc. chim.*, 1908, [iv], **3**, 829; 1909, [iv], **5**, 950; O. Becker and Thorpe, *J.*, 1922, **121**, 1303; Ekeley and Howe, *J. Amer. Chem. Soc.*, 1923, **45**, 1917; Ekeley and Carpenter, *ibid.*, 1924, **46**, 446; Abbott, Kon, and Satchell, *J.*, 1928, 2514).

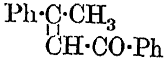
Preparation of Diacetone Alcohol.—A 2-l. flask is fitted with a rubber bung carrying a Soxhlet extractor fitted with a very efficient condenser. Acetone (1,500 c.c.) is placed in the flask with some pieces of porous pot to facilitate boiling. The Soxhlet contains two extraction thimbles each about three-quarters full of crystalline barium hydroxide, the remainder of the space being filled with glass wool to prevent any of the barium hydroxide being carried over. The flask is heated in a water-bath and the reaction is continued till the acetone no longer refluxes when the water-bath is boiling vigorously (95—120 hours). The contents of the flask are now distilled from an oil bath at 125° through an efficient fractionating column till acetone ceases to come over. The residue is then fractionated under reduced pressure, b. p. 71—74°/23 mm.—yield 850 g. (Conant and Tuttle, *Organic Syntheses*, 1922, **1**, 45).

Condensations of the mesityl oxide and mesitylene type take place not only in the case of the aliphatic ketones, but also in those of acetophenone and *cyclo*hexanone. Thus *cyclo*hexanone yields (VII) by the action of hydrogen chloride (Wallach, *Ber.*, 1907, **40**, 70); heating with alcoholic sulphuric acid yields (VIII) (Mannich, *Ber.*, 1907, **40**, 153). Acetophenone by the action of iodine or zinc chloride similarly undergoes the mesityl oxide type of condensation to give dypnone (IX). Triphenyl benzene (X) can also be prepared by more drastic conditions.



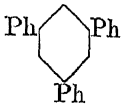
(VII.)





$$\begin{matrix}Ph\cdot C\cdot CH_3\\ \|\\ CH\cdot CO\cdot Ph\end{matrix}$$

(IX.)



(VIII.) (X.)

(2) *Reaction of the Carbonyl Group with Nitroparaffins and Nitriles.*—Benzaldehyde and some other aromatic aldehydes condense with nitromethane and other primary nitroparaffins to give nitro-olefins according to the scheme

$$Ph\cdot CHO + R\cdot CH_2\cdot NO_2 \longrightarrow Ph\cdot CH{:}CR\cdot NO_2.$$

The condensation has been effected under the influence of a small amount of zinc chloride (Priebs, *Annalen*, 1884, **225**, 321), or potassium hydroxide solution (Thiele and Haeckel, *ibid.*, 1902, **325**, 7). Primary or secondary aliphatic amines act as very convenient condensing agents (Knoevenagel and L. Walter, *Ber.*, 1905, **37**, 4502).

Preparation of ω-Nitrostyrene.—A solution of purified benzaldehyde (53 g.) and nitromethane (31 g.) in 200 c.c. of methyl alcohol is cooled in a freezing mixture, and a solution of 21 g. of sodium hydroxide in 50 g. of ice and water is added cautiously. The reaction mixture is stirred mechanically and the addition of the alkali controlled so that the temperature is maintained at 10—15°. The first few c.c. of alkali must be added cautiously, since there is an induction period. As the condensation proceeds, a bulky white precipitate forms rapidly. If the mixture becomes too thick for stirring, it is diluted by the addition of more methyl alcohol. The reaction is complete when a test portion gives a clear solution in water. It is then diluted with about 300 c.c. of ice-water and neutralised by running the solution into a stirred solution of 100 c.c. of concentrated hydrochloric acid in 150 c.c. of water. The crude nitrostyrene separates as a yellow crystalline mass. This is collected, washed with water, and purified by crystallisation from ethyl alcohol, m. p. 57—58°—yield about 60 g. (Thiele and Haeckel, *loc. cit.*; Worral, *Organic Syntheses*, 1929, **9**, 66).

A similar process has been described by Rosenmund (*Ber.*, 1909, **42**, 4780) for the preparation of *p*-methoxy-ω-nitrostyrene.

Preparation of α-Anisylidene-nitroethane (*β*-p-*methoxyphenyl α-methyl α-nitroethylene*).—Nitroethane (1 g.) and anisaldehyde (2 g.) are mixed and 2 drops of ethylamine added. After keeping at room temperature for 2 or 3 days, crystals begin to separate; after about a fortnight, the separation is complete. The crystals are collected and purified by crystallisation from light petroleum, m. p. 48° (Knoevenagel and Walter, *loc. cit.*).

Benzyl cyanide and many of its substitution products can condense with benzaldehyde, furfuraldehyde, anisaldehyde, and similar aldehydes to yield aryl-substituted cyanoethylenes.

$$\mathrm{Ph{\cdot}CHO + Ph{\cdot}CH_2{\cdot}CN \longrightarrow Ph{\cdot}CH{:}C(CN){\cdot}Ph}$$

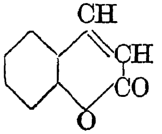
Preparation of aβ-Diphenyl a-cyanoethylene.—About 5 c.c. of a 20% solution of sodium ethoxide are added to a well-stirred mixture of benzaldehyde (9·5 g.) and benzyl cyanide (10 g.). The reaction mixture becomes warm and a white crystalline mass commences to separate. After keeping for some time, the precipitate is collected, washed with water, and then with alcohol to remove the aldehyde and nitrile which have not reacted. The product is purified by crystallisation from boiling alcohol, m. p. 86° (Frost, *Annalen*, 1889, **250**, 157).

(3) *Reaction of the Carbonyl Group with Acids and Esters.*—The experimental conditions for the reaction of an aldehyde with acids may be divided broadly into two groups: (*a*) reactions grouped together as the Perkin reaction in which a salt of the acid of the type $\mathrm{R{\cdot}CH_2{\cdot}CO_2H}$ (R is either alkyl or aryl) is heated with a suitable aromatic aldehyde in presence of acetic anhydride or the anhydride of the appropriate acid; (*b*) the reaction is effected between malonic acid and an aldehyde in a suitable solvent or catalysed by an amine or similar condensing agent.

By means of the Perkin reaction, cinnamic acid and its substituted derivatives can readily be prepared. Thus benzaldehyde heated with acetic anhydride and sodium acetate yields cinnamic acid. With propionic anhydride and sodium propionate, α-methylcinnamic acid is formed. α-Phenylcinnamic acid is similarly obtained from phenylacetic acid. The condensation in this reaction always occurs at the α-carbon atom (W. H. Perkin, sen., *J.*, 1877, **31**, 388), and the reaction is represented by the equation

$$\mathrm{Ph{\cdot}CHO + R{\cdot}CH_2{\cdot}CO_2H \longrightarrow Ph{\cdot}CH{:}CR{\cdot}CO_2H + H_2O.}$$

The homologues of benzaldehyde and its nitro- and halogen nuclear substituted derivatives, furfuraldehyde, and thienyl aldehyde react like benzaldehyde to give unsaturated acids. In general, the aliphatic aldehydes do not give satisfactory products by this reaction, although some of the higher aliphatic aldehydes have been used successfully. When salicylaldehyde and other *o*-phenolic aldehydes are condensed with suitable acids, there is an elimination of the elements of water between the carboxyl of the unsaturated acid and the phenolic hydroxyl yielding a lactone. Salicylaldehyde yields coumarin:



Preparation of Cinnamic Acid.—A mixture of 20 g. of freshly-distilled benzaldehyde, 10 g. of anhydrous powdered sodium acetate, and 30 g. of acetic anhydride contained in a small round-bottomed flask fitted with a vertical air condenser, is heated for 8 hours at 180° by means of an oil-bath. The reaction product is then poured, while still hot, into an excess of sodium carbonate solution. The unchanged benzaldehyde is removed by distillation in steam and the residual solution filtered from resinous impurities. Cinnamic acid is precipitated from the filtrate by the addition of an excess of dilute hydrochloric acid. It is collected by filtration and purified by crystallisation from hot water, m. p. 133°—yield 15—20 g. (Bertagnini, *Annalen*, 1856, **100**, 126; Perkin, *J.*, 1868, **21**, 53).

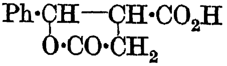
Preparation of a-o-Nitrophenylcinnamic Acid.—*o*-Nitrobenzaldehyde (16 g.), the sodium salt of phenylacetic acid (16 g.), zinc chloride (2 g.), and acetic anhydride (180 g.) are heated together for 5 hours at 120° in an oil-bath. The product is a reddish crystalline paste, which is boiled with 180 c.c. of water to destroy the excess of acetic anhydride, then diluted with 750 c.c. of water. The product is filtered off, dried, and purified by crystallisation from 120 g. of hot toluene. On cooling, the acid separates as almost colourless needles, m. p. 193—195° after further crystallisation—yield about 50% of theoretical (Pschorr, *Ber.*, 1896, **29**, 497).

Preparation of Coumarin.—A mixture of salicylaldehyde (40 g.), acetic anhydride (60 g.), anhydrous sodium acetate (65 g.), and iodine (1 g.) is heated under reflux for 2 hours at 120° and then for 5 hours at 180—190°. The product is then poured into water and extracted with ether. After freeing the ethereal solution from salicylaldehyde by shaking with concentrated sodium bisulphite solution, the ether solution is washed with water, dried in contact with calcium chloride, and the solvent evaporated. The residue of crude coumarin is distilled under reduced pressure. Coumarin is collected at 106°/1 mm. It is finally purified by crystallisation from light petroleum (b. p. 60—80°), when it is obtained as white needles, m. p. 67°—yield about 20 g.

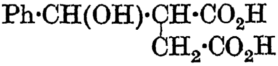
The Perkin reaction has been extended to the reaction of aldehydes with succinic acid and some of its alkyl-substituted derivatives. The general conditions consist in heating the sodium salt of the acid with acetic anhydride and the appropriate aldehyde. The product varies considerably, consisting of a paraconic acid or the corresponding $\beta\gamma$-unsaturated acid derived by the loss of carbon dioxide and water from the paraconic acid, or a mixture of both types of products. Thus benzaldehyde heated with sodium succinate and acetic anhydride for 5 hours at 125° yields a mixture of phenyl*iso*crotonic (XI) and phenylparaconic acids (XII) (Fittig and Jayne, *Annalen*, 1882, **216**, 99). At higher temperatures the yield of phenyl*iso*crotonic acid increases at the expense of the paraconic acid (compare W. H. Perkin, sen., *J.*, 1877, **31**, 394).

$$\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H} \quad \text{(XI.)}$$

(XII.)



$$\begin{array}{l}\mathrm{Ph{\cdot}CH{-}CH{\cdot}CO_2H}\\ \quad \mathrm{O{\cdot}CO{\cdot}CH_2}\end{array}$$



$$\begin{array}{r}\mathrm{Ph{\cdot}CH(OH){\cdot}CH{\cdot}CO_2H}\\ \mathrm{CH_2{\cdot}CO_2H}\end{array}$$

(XIII.)

Aliphatic aldehydes have been employed successfully for the production of alkyl paraconic acids.

In the preparation of the paraconic acids, a hydroxy-acid (XIII) seems to be the intermediate product which readily forms the lactonic acid (XII). It might be inferred that also in the formation of cinnamic acid a hydroxy acid is formed as an intermediate product which eliminates the elements of water on heating. The reaction, on this hypothesis, would then be similar in type to the aldol-crotonaldehyde reaction of acetaldehyde. Indirect evidence in favour of this hypothesis is provided by the work of Fittig and his co-workers. They found that *iso*butyric acid condenses with benzaldehyde to give the hydroxy-acid (XIV).

$$\mathrm{Ph{\cdot}CHO + (CH_3)_2CH{\cdot}CO_2H \longrightarrow Ph{\cdot}CH(OH){\cdot}CMe_2{\cdot}CO_2H} \quad \text{(XIV.)}$$

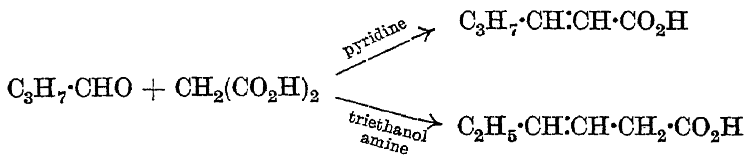
They also showed that the hypothetical intermediate product $\mathrm{Ph{\cdot}CH(OH){\cdot}CH_2{\cdot}CO_2H}$ in the preparation of cinnamic acid loses water below the temperature at which benzaldehyde reacts with sodium acetate (Fittig and Slocum, *Annalen*, 1885, **227**, 53; Fittig and Ott, *ibid.*, p. 61). Other views of the mechanism of this reaction have, however, been advanced (W. H. Perkin, sen., *J.*, 1886, **49**, 317; Nef, *Annalen*, 1897, **298**, 309; Michael, *Ber.*, 1901, **34**, 918; Conrad and Bischoff, *Annalen*, 1880, **204**, 183).

The reaction between aldehydes and malonic acid or its esters proceeds more easily than that between the corresponding aldehydes and monobasic acids. It can be effected in acetic acid solution or under the condensing influence of amines, and leads to the formation of an alkylidene malonic acid, which readily loses carbon dioxide to give an unsaturated monobasic acid. This process is of considerable value in the synthesis of unsaturated aliphatic acids.

Acetaldehyde reacts with malonic acid in pyridine solution to give crotonic acid. Propionaldehyde and *n*-butaldehyde react similarly to give αβ-unsaturated acids according to the scheme

$$\mathrm{R{\cdot}CHO + CH_2(CO_2H)_2 \longrightarrow R{\cdot}CH{:}CH{\cdot}CO_2H + CO_2.}$$

From a thorough investigation of this condensation it appears that *n*-butaldehyde gives exclusively the αβ-unsaturated acid. The action of other basic condensing agents is remarkable, since considerable amounts of the isomeric βγ-unsaturated acid are formed, dimethylaniline and triethanolamine giving rise to the almost pure βγ-acid. Propaldehyde and *iso*valeraldehyde behave similarly.



$$\begin{tikzcd}
 & \mathrm{C_3H_7{\cdot}CH{:}CH{\cdot}CO_2H} \\
\mathrm{C_3H_7{\cdot}CHO + CH_2(CO_2H)_2} \arrow[ur, "\text{pyridine}"] \arrow[dr, "\text{triethanol amine}"'] & \\
 & \mathrm{C_2H_5{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H}
\end{tikzcd}$$

(Boxer and Linstead, *J.*, 1931, 740; compare Zaar, *Ber. Schimmel*, 1929, 297; v. Auwers, *Annalen*, 1923, **432**, 58).

It should be noted that v. Auwers has isolated a small amount of β-hydroxy-acid as by-product in the condensation of acetaldehyde and of *n*-butaldehyde with malonic acid in pyridine solution.

Preparation of Crotonic Acid.—An ethereal solution of acetaldehyde is prepared by heating 60 g. of paracetaldehyde with a few drops of sulphuric acid in a water-bath. The acetaldehyde thus evolved is passed upwards through a short inclined condenser to remove any paraldehyde. It is dried by passage through a tube containing calcium chloride and collected in 60 c.c. of ether cooled by an external bath of ice-water.

To this solution 26 g. of powdered malonic acid are added, followed by 20 g. of pyridine. The mixture is kept for 2 days at 0° and then at room temperature for a day. The ether is then removed and the residue heated till no more carbon dioxide is evolved. Solution of the residue thus obtained followed by precipitation with concentrated hydrochloric acid yields crotonic acid. A further amount is obtained by ether extraction of the filtrate—yield 18 g. It is purified by crystallisation from light petroleum (b. p. 60—80°), m. p. 72° (Letch and Linstead, *J.*, 1932, 455; Henle, *Anleitung f. d. Organisch-Chemische Praktikum*, 1927, p. 188).

Preparation of Sorbic Acid.—$CH_3\cdot CH:CH\cdot CH:CH\cdot CO_2H$. Crotonaldehyde (40 g.), malonic acid (60 g.), and pyridine (60 g.) are mixed and heated on a water-bath. There is a lively evolution of carbon dioxide, and when this ceases (about 3 hrs.) the mixture is cooled in ice and an excess of dilute sulphuric acid added. The crystalline mass of sorbic acid which separates is collected after keeping. A further amount is obtained by ether extraction of the filtrate—yield 20 g. Sorbic acid crystallises from hot water in long needles, m. p. 134° (Doebner, *Ber.*, 1900, **33**, 2140).

✓ *Preparation of Cinnamic Acid.*—Equimolecular proportions of malonic acid and benzaldehyde are heated on a water-bath with 2 mol. props. of 8% alcoholic ammonia till the solution is clear. The alcohol is then removed by distillation and the residue heated on the water-bath till the evolution of carbon dioxide ceases. The product is then dissolved in hot water and the cinnamic acid precipitated by the addition of dilute hydrochloric acid—yield 80—85% of theory (Knoevenagel, *Ber.*, 1898, **31**, 2604).

Preparation of Cinnamylidenemalonic acid.—Equal weights of cinnamaldehyde, glacial acetic acid, and malonic acid are heated together on a water-bath for 9 hours, the mixture being shaded from light. The mass sets to a paste which is drained and washed with chloroform. It is crystallised from absolute alcohol, m. p. 208°—yield about 140—200 g. from 200 g. of malonic acid (Liebermann, *Ber.*, 1895, **28**, 1439; compare Thiele and Meisenheimer, *Annalen*, 1899, **306**, 252).

Cyanoacetic acid can be used for these condensations instead of malonic acid. The reaction proceeds similarly to give either an α-cyano-unsaturated acid or an unsaturated nitrile if the experimental conditions are arranged so as to eliminate carbon dioxide.

$$R\cdot CHO + CH_2(CN)\cdot CO_2H \longrightarrow R\cdot CH:C(CN)\cdot CO_2H \longrightarrow R\cdot CH:CH\cdot CN$$

Preparation of α-Cyano-Δ^{α}-n-hexenoic Acid.—Molecular proportions of cyanoacetic acid and freshly distilled butaldehyde are heated on a water-bath with 1/50 mol. of piperidine for 4 hours. The product is extracted with dilute sodium bicarbonate solution and the crude cyano-acid is precipitated as a brown viscous oil by acidifying the extract.

It is obtained crystalline by heating at 70—80° under reduced pressure for some time, then by slow evaporation of an ethereal solution of the product, the acid separates as a coarse white powder. It crystallises from benzene in needles, m. p. 102° (Letch and Linstead, *J.*, 1932, 450).

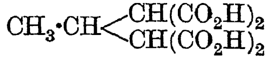
The condensation of benzaldehyde and its homologues with esters of the fatty acids can be effected quite easily by Claisen's method of using metallic sodium as the condensing agent.

Preparation of Ethyl Cinnamate (a).—To an excess of ethyl acetate free from alcohol, sodium wire is added and then benzaldehyde cautiously and with cooling (1 mol. prop. aldehyde for 1 atom. prop. of sodium). When all the sodium has reacted, the mixture is kept for some time, then sufficient dilute acetic acid is added to combine with all the sodium. The ester layer is separated, washed, and dried. Fractionation gives unchanged ethyl acetate and ethyl cinnamate, b. p. 260—270°—yield about 100—110% of the weight of benzaldehyde used.

The reaction appears to be of general application for the preparation of α-alkyl and α-aryl cinnamic acids (Claisen, *Ber.*, 1890, **23**, 976; Posner, *J. pr. Chem.*, 1910, [ii], **82**, 435).

(b) 29 G. of clean sodium and 400 c.c. xylene are placed in a 2-l. two-necked flask fitted with a short reflux condenser and a mechanical stirrer. The flask is heated in an oil-bath till the sodium has melted, when the stirrer is started and the oil-bath removed. The stirring is continued till the sodium has been converted into a powder. The xylene is then poured off and 455 c.c. of ethyl acetate with 3 c.c. of absolute alcohol are added. The contents of the flask are then cooled to 0° and 106 g. of pure benzaldehyde added slowly over a period of 1½—2 hrs., the temperature of the reaction mixture keeping below 10°. The stirring is continued till practically all the sodium has reacted, when 90—95 c.c. of glacial acetic acid are added and the mixture is cautiously diluted with water. The ester layer is separated, the aqueous portion extracted with about 30 c.c. of ethyl acetate. The combined ester portions are washed with 300 c.c. of 6*N*-hydrochloric acid and dried over sodium sulphate. The bulk of the ethyl acetate is removed on the water-bath and the residue fractionated under reduced pressure. Ethyl cinnamate is collected at 128—133°/6 mm.—yield 120—130 g. (Claisen, *loc. cit.*; Marvel and W. B. King, *Organic Syntheses*, 1929, **9**, 38).

Malonic ester, and in general all esters containing the groupings $-CO\cdot CH_2\cdot CO-$ or $-CO\cdot CH_2\cdot CN$, react with aldehydes more readily than esters of the monobasic fatty acids. The condensation can take place with either aromatic or aliphatic aldehydes, and is generally brought about by the addition of a small amount of ammonia, dimethylamine, piperidine, or a similar amine. Under these conditions the aliphatic aldehydes yield principally saturated esters by reaction with 2 molecules of malonic ester, while aromatic aldehydes give rise to unsaturated esters by the same reaction. Thus acetaldehyde reacts with malonic ester to give the ester (XV); formaldehyde, propaldehyde, and butaldehyde behave similarly. Benzaldehyde gives chiefly benzalmalonic ester (XVI).



$$CH_3\cdot CH\left\langle\begin{matrix}CH(CO_2H)_2\\CH(CO_2H)_2\end{matrix}\right.$$

(XV.)

$$Ph\cdot CH{:}CH(CO_2H)_2$$

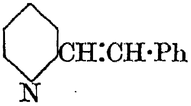
(XVI.)

Preparation of Benzalmalonic Ester.—Malonic ester (100 g.)—dried by distillation under reduced pressure over anhydrous sodium carbonate—and freshly distilled benzaldehyde (70 g.) are mixed and 2 g. of piperidine added. The mixture is kept in a corked flask for 2 days and then heated on a water-bath for 12 hours. The reaction mixture is then diluted with ether, washed with water and acid, dried over anhydrous sulphate, and distilled under reduced pressure. The benzal malonic ester is collected at 185—186°/11 mm., 70% yield. It solidifies on cooling (Knoevenagel, *Ber.*, 1898, **31**, 2591).

Cyanoacetic ester undergoes a similar condensation with aldehydes. Benzaldehyde gives α-cyanocinnamic ester (Carrick, *J. pr. Chem.*, 1892, [ii], **45**, 500). Acetone and some cyclic ketones react with ethyl acetoacetate in a similar manner (Merling and Welde, *Annalen*, 1909, **366**, 131 *et seq.*; Jupp, Kon, and Lockton, *J.*, 1928, 1638).

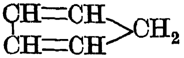
The Knoevenagel condensation in which a carbonyl group reacts with $-CO{\cdot}CH_2{\cdot}CO-$ grouping under the influence of a small amount of primary or secondary amine has been extended to the condensation of aliphatic and aromatic aldehydes with β-keto-esters (as acetoacetic ester or benzoylacetic ester) and with 1 : 3-diketones (as benzoyl acetone). A list of references to work on this condensation earlier than 1904 is given by Knoevenagel (*Ber.*, 1904, **37**, 4461).

The condensation of benzaldehyde with 2 : 4-dinitrotoluene has already been referred to (p. 55) (compare Ruggli, Zimmermann, and Thouvay, *Helv. Chim. Acta*, 1931, **14**, 1250). A similar type of condensation is shown by quinaldine and α-methylpyridine, which by reaction with aldehydes give rise to derivatives of the type



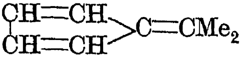
(Ladenburg, *Ber.*, 1886, **19**, 439, 2578; Shaw, *J.*, 1924, **125**, 2363).

Condensation of the carbonyl group with the grouping $CH_2{<}\genfrac{}{}{0pt}{}{C=}{C=}$ can be effected under the influence of alcoholic potash. Thus *cyclo*pentadiene (XVII) reacts with acetone to give dimethylfulvene (XVIII); benzophenone and acetophenone behave similarly to acetone (Thiele, *Ber.*, 1900, **33**, 666). Fluorene (XIX) and indene (XX) yield analogous compounds with aldehydes (Thiele and Bühner, *Annalen*, 1906, **347**, 249; Thiele and Henle, *ibid.*, p. 296; Sieglitz, *Ber.*, 1919, **52**, 1514; 1920, **53**, 1232; Wislicenus and Hentrich, *Annalen*, 1924, **436**, 11).



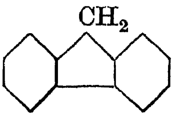
$\begin{matrix}CH{=}CH\\ CH{=}CH\end{matrix}{>}CH_2$

(XVII.)

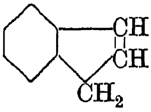


$\begin{matrix}CH{=}CH\\ CH{=}CH\end{matrix}{>}C{=}CMe_2$

(XVIII.)

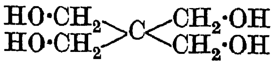


(XIX.)

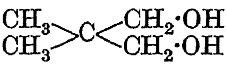


(XX.)

(XXI.)



$\begin{matrix}HO{\cdot}CH_2\\ HO{\cdot}CH_2\end{matrix}{>}C{<}\begin{matrix}CH_2{\cdot}OH\\ CH_2{\cdot}OH\end{matrix}$



$\begin{matrix}CH_3\\ CH_3\end{matrix}{>}C{<}\begin{matrix}CH_2{\cdot}OH\\ CH_2{\cdot}OH\end{matrix}$

(XXII.)

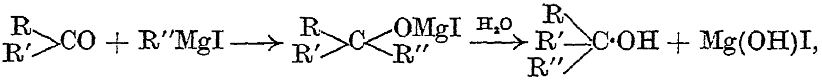
(XXIII.) $(HO{\cdot}CH_2)_2CH{\cdot}CO{\cdot}CH(CH_2{\cdot}OH)_2$

In the foregoing sections the condensations of acetaldehyde and its homologues and of aromatic aldehydes have been reviewed. It is convenient here to consider the condensations of formaldehyde separately, for it is frequently abnormal in its behaviour. Thus it condenses with aliphatic aldehydes to give products which may contain several formaldehyde residues. Thus acetaldehyde and formaldehyde give pentaerythritol (XXI); isobutaldehyde gives the glycol (XXII); from acetone (XIII) is obtained (Tollens and Wigand, *Annalen*, 1891, **265**, 316; Apel and Tollens, *ibid.*, 1895, **289**, 36; Tollens, *ibid.*, 1893, **276**, 82).

Reaction of formaldehyde with nitromethane results in the replacement of all 3 hydrogens of the methyl group by $-CH_2{\cdot}OH$. With the higher nitroparaffins there is a tendency for more than one of the hydrogens to be replaced by $-CH_2OH$ (L. Henry, *Compt. rend.*, 1895, **120**, 1265; **121**, 210; *Rec. trav. chim.*, 1897, **16**, 189, 193).

(*e*) *Reaction of the Carbonyl Group with the Grignard Reagent.*

Alkyl- and aryl-magnesium halides react with the carbonyl group to give additive compounds which are decomposed by water and dilute acids to yield alcohols.



$$\begin{matrix}R\\R'\end{matrix}\!>CO + R''MgI \longrightarrow \begin{matrix}R\\R'\end{matrix}\!>C<\!\begin{matrix}OMgI\\R''\end{matrix} \xrightarrow{H_2O} \begin{matrix}R\\R'\\R''\end{matrix}\!\!-\!C{\cdot}OH + Mg(OH)I,$$

where R, R′, R″ are aryl or alkyl groups or hydrogen.

It is thus seen that a ketone gives rise to a tertiary alcohol as the normal product; aldehydes yield secondary alcohols, while primary alcohols result if formaldehyde is used. These reactions are therefore of considerable importance in syntheses. They are illustrated by the following examples.

Preparation of tert.-*Butyl Alcohol.*—An ethereal solution of methyl magnesium iodide is prepared from 8·2 g. of magnesium turnings and 49 g. of methyl iodide in 25 c.c. of dry ether (see p. 374).

A solution of dry acetone (20 g.) in an equal volume of dry ether is added drop by drop to the cooled solution of methyl magnesium iodide. The precipitate which is formed initially dissolves, but as more methyl magnesium iodide is added it separates as a greyish viscous mass at the bottom of the flask.

The reaction is completed by keeping overnight, when the product is decomposed by the addition of ice. When the precipitate is white, sufficient 30% acetic acid is added to dissolve it. The ethereal layer is separated, the ether evaporated, and the residue added to the aqueous portion, which is distilled in steam till no more butyl alcohol distils over. The distillate is saturated with potassium carbonate, the alcohol separated and dried over powdered potassium carbonate. The alcohol obtained by the distillation of the dried material contains one molecule of water. This can be removed by prolonged contact with barium oxide or by gentle distillation over the requisite amount of sodium (Grignard, *Ann. Chim.*, 1901, [vii], **24**, 470; Wren, *Organo-metallic Compounds of Zinc and Magnesium*, 1913, p. 2).

Preparation of sec.-*Butyl Alcohol.*—A Grignard reagent is prepared from 72 g. of magnesium turnings and 340 g. of ethyl bromide in ether.

The flask containing the prepared reagent is cooled in a freezing mixture of ice and salt, and a solution of 150 g. of acetaldehyde in twice its volume of ether is added gradually from a tap funnel during 2 hours. After keeping overnight, the unchanged acetaldehyde and some of the ether are distilled off, by heating the flask in a water-bath at about 40°.

The residue is then poured, with stirring, into a mixture of ice and ammonium chloride. The ethereal layer is separated off, and distilled to remove the ether. The residue and also the aqueous portion of the product are steam distilled, the distillates saturated with potassium carbonate, and the alcohol separated and dried over freshly ignited potassium carbonate (Pickard and Kenyon, *J.*, 1913, **103**, 1938).

By a similar process these authors have prepared a large number of secondary alcohols. For experimental details the original papers should be consulted (*J.*, 1911, **99**, 55; 1912, **101**, 628).

Preparation of sec.-*Butyl Carbinol.*—The Grignard reagent is prepared from 325 g. of *sec.*-butyl bromide and 57 g. of magnesium. To the prepared reagent, 70 g. of trioxymethylene are added all at once. After keeping the mixture overnight, it is heated under reflux for 24 hours.

The ethereal solution is then decomposed little by little by the addition of diluted sulphuric acid, and the aqueous layer is extracted several times with ether. The ethereal extracts, after washing with saturated potassium carbonate solution, are dried over anhydrous potassium carbonate, and the ether is removed by careful distillation through a fractionating column. The residue is fractionated.

After a preliminary fraction collected up to 127° consisting of moist alcohol, the pure alcohol is collected at 127—131°, and may amount to 140 g. A fraction, b. p. 195—205°, is also obtained, and consists of the diamyl ether of formaldehyde.

In this preparation it is essential that the trioxymethylene should be dry. It is recommended that the commercial product be dried at 100° under reduced pressure and then stored in a vacuum desiccator over phosphorus pentoxide (Freundler and Damond, *Bull. Soc. chim.*, 1906, [iii], **35**, 110).

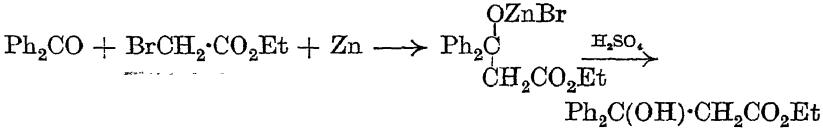
This method has the disadvantage that trioxymethylene is sparingly soluble in ether, and consequently reacts but slowly. A modification which obviates prolonged refluxing consists in passing gaseous formaldehyde into the Grignard reagent. A suitable arrangement of apparatus and experimental conditions for this reaction are described by Ziegler (*Ber.*, 1921, **54**, 738), Ziegler and P. Tiemann (*Ber.*, 1922, **55**, 3406), Wood and Scarf (*J.S.C.I.*, 1923, **42**, 13T).

Davies and Kipping have shown (*J.*, 1911, **99**, 296) that the Grignard reaction may be simplified by allowing the mixture of alkyl halide and ketone to react with magnesium covered by a layer of ether containing a small amount of preformed alkyl magnesium halide. The reaction is very convenient. It has, however, as yet received only a limited application. In addition to condensation with ketones and aldehydes it has been shown to give good results with esters and some inorganic chlorides.

Preparation of Triethylcarbinol.—About 1 c.c. of ethyl bromide is added to 12 g. of magnesium turnings covered with dry ether to which two very small crystals of iodine have been added. A vigorous reaction sets in. When it shows signs of abating, a mixture of diethyl ketone (43 g.) and ethyl bromide (53 g.) diluted with an equal volume of ether is added gradually from a dropping funnel. A vigorous reaction follows the addition of the solution, and it is advisable to keep the mixture gently shaken during the reaction. When all the solution has been added the reaction mixture is heated under reflux for 2 or 3 hours. Eventually the mixture is decomposed by the addition of ice and dilute sulphuric acid. The ethereal layer is separated, dried over potassium carbonate, and the ether distilled off through a fractionating column. On distillation the residue yields crude triethyl carbinol, b. p. 131—141°.

This process can be applied to methyl ethyl ketone, ethyl propyl ketone, and acetophenone, but it fails with acetone.

Aldehydes and ketones can react with α-bromo- or iodo-esters of fatty acids in the presence of zinc to yield β-hydroxy-acids (Reformatski and co-workers, *Ber.*, 1887, **20**, 1210; 1895, **28**, 2838; *J. Russ. Phys. Chem. Soc.*, 1890, **22**, 44; *J. pr. Chem.*, 1896, [ii], **54**, 469). The reaction is exemplified by the condensation of benzophenone with bromoacetic ester.



$$Ph_2CO + BrCH_2{\cdot}CO_2Et + Zn \longrightarrow Ph_2\overset{\displaystyle OZnBr}{\underset{\displaystyle CH_2CO_2Et}{C}} \xrightarrow{H_2SO_4} Ph_2C(OH){\cdot}CH_2CO_2Et$$

Under the conditions originally described by Reformatski, α-chloro-esters do not appear to react. Recently, however, Nieuwland and Daly (*J. Amer. Chem. Soc.*, 1931, **53**, 1842) found that the reaction proceeds if copper powder is used in conjunction with zinc.

Preparation of the Ethyl Ester of β-Hydroxy-ββ-diphenylpropionic Acid.—A mixture of benzophenone (18·2 g.), bromoacetic ester (20 g.), and zinc (8 g.) in dry benzene (90 c.c.) is cautiously heated under an efficient reflux condenser till the reaction commences. The reaction mixture must then be cooled in ice-water to prevent the reaction becoming too violent. The cooling must not be sufficient to stop the condensation; it should allow the reaction to proceed briskly without becoming violent. The condensation is finally completed by boiling under reflux for ¾ hour. The product is then treated with ice-cold dilute sulphuric acid. The benzene layer is separated, washed with water, and dried. After distilling the solvent from it, the residue of β-hydroxy-ester solidifies. It is purified by crystallisation from aqueous alcohol, m. p. 87°—yield about 17 g. (Rupe and Busolt, *Ber.*, 1907, **40**, 4537).

Preparation of the Ethyl Ester of β-Hydroxy-β-phenyl-β-methylpropionic Acid.—A mixture of acetophenone (35 g.), chloroacetic ester (38 g.), benzene (35 g.), zinc (18 g.), and copper powder (3 g.) is heated under reflux by a small flame till the vigorous reaction which sets in has subsided. The mixture must be shaken frequently during the heating so that the zinc does not cake. The reaction mixture is then cooled and treated with ice-cold 20% sulphuric acid till all the zinc has dissolved. The upper layer is then separated and the lower aqueous layer extracted with ether. The ether extracts and the upper layer are combined, dried in contact with anhydrous sodium sulphate, and the solvents removed by distillation. The residual ester is then distilled under reduced pressure. The pure product is collected at 146—147°/15 mm. (Nieuwland and Daly, *loc. cit.*).

(f) *Formation of Acetals.*

The aldehydes and ketones by suitable processes yield acetals, the carbonyl group being converted into a diether $>C(OAlk.)_2$. With many aldehydes this can be accomplished by treatment with an alcohol containing hydrogen chloride (E. Fischer and Giebe, *Ber.*, 1897, **30**, 3053; 1898, **31**, 545) or ammonium chloride (R. D. Haworth and Lapworth, *J.*, 1922, **121**, 79). In this process an equilibrium is attained (Delépine, *Bull. Soc. chim.*, 1901, [iii], **25**, 574),

$$R{\cdot}CHO + 2R'{\cdot}OH \longrightarrow R{\cdot}CH(OR')_2 + H_2O.$$

By careful attention to the factors which influence this reaction,

R. D. Haworth and Lapworth (*loc. cit.*) have considerably improved the yields of acetal obtained by Fischer's method.

Preparation of Diethylacetal of Benzaldehyde.—Benzaldehyde is mixed with about 8 volumes of absolute ethyl alcohol containing 1% of dry hydrogen chloride. After keeping for about 2 days at room temperature to attain equilibrium, alcoholic sodium ethoxide is added till the solution is neutral to phenolphthalein. The solvent is removed under reduced pressure at 30°. The residue is freed from benzaldehyde by shaking it with sodium hydrogen sulphite to which enough sodium carbonate has been added to remove all odour of sulphur dioxide. The undissolved oil is extracted with ether, dried over potassium carbonate, and fractionated under reduced pressure, b. p. 222°/760 mm.—yield 55%.

Alcoholic hydrogen chloride may be replaced by alcohol containing about 0·6% of ammonium chloride. The subsequent operations are those just described.

Under similar conditions—except that the time required for reaching equilibrium is from 2 to 9 days—the diethyl acetals of *iso*valeraldehyde, anisaldehyde, *m*-nitrobenzaldehyde, cinnamaldehyde, piperonal have been prepared (Haworth and Lapworth, *loc. cit.*).

The Fischer process of acetalisation does not succeed with ketones. They can, however, be converted into acetals by Claisen's methods, which depend on reaction with alcohol containing formino-ether hydrochloride or orthoformic ester. Aldehydes can also be acetalised by these methods (Claisen, *Ber.*, 1896, **29**, 1005; 1898, **31**, 1010; 1907, **40**, 3903).

Preparation of Keto-acetals (Formino-ether Hydrochloride Process).—The following general directions are given by Claisen. Formino-ether hydrochloride (1¼ mol. props.) is added to a well-cooled solution of the ketone in an excess of absolute alcohol (at least 5 mol. props.). The reaction mixture is kept at first in the ice-chest and then at room temperature for from 4 to 8 days. An excess of ether is then added, the precipitate of ammonium chloride collected, and the filtrate decomposed by the addition of ice-water containing a few drops of ammonia. The ethereal solution is separated, dried over potassium carbonate, and then distilled under reduced pressure. With acetals of low boiling point it is advantageous to fractionate the ethereal solution through an efficient column.

Aldehydes can be acetalised by this method. With acetaldehyde it is necessary to cool the reaction mixture strongly in order to moderate the violence of the reaction.

Some unsaturated aldehydes add the elements of alcohol to the double bond during the formation of the acetal.

Preparation of Acetone Diethyl Acetal (Orthoformic Ester Process).—Absolute alcohol (27·6 g.) is boiled for some time with 1 g. of finely-powdered ammonium chloride to obtain as much as possible in solution. On cooling, acetone (11·6) g. and orthoformic ester (32·5 g.) are added and the solution is kept at room temperature for about 8 days. It is then diluted with ether and sufficient water (made alkaline with a few drops of ammonia) is added to dissolve the ammonium chloride. The ethereal solution is dried and carefully fractionated through a column, b. p. 114°—yield 21 g. of crude, 18 g. of pure acetone diethyl acetal.

Preparation of Benzaldehyde Diethyl Acetal.—A mixture of benzaldehyde (37·5 g.), orthoformic ester (57 g.), and ethyl alcohol (49 g.) is heated under reflux for 10 minutes after the addition of 0·75 g. of powdered ammonium chloride. The excess of alcohol and of orthoformic ester is removed by distillation through a column and the residue treated with water and shaken with ether. After drying the ethereal solution over potassium carbonate, it is distilled. Benzaldehyde diethyl acetal passes over at 217—223°—yield 62 g.

The ammonium chloride can be replaced by a trace of concentrated hydrochloric acid or by 0·3 g. of ferric chloride, or 0·3 g. of potassium hydrogen sulphate.

Helferich and Hausen (*Ber.*, 1924, **57**, 795) describe a new method for the preparation of acetals of aldehydes and ketones. It is based on the reaction of the appropriate orthosilicic ester with the aldehyde or ketone in alcoholic solution. The following is a general description of this reaction.

The aldehyde or ketone (1 mol. prop.) dissolved in 2—3 mol. props. of the appropriate alcohol is mixed with 1·1 mol. props. of the appropriate ester of orthosilicic acid and a few drops of alcoholic hydrogen chloride are added.

The mixture may then be kept for several days at room temperature or heated under reflux. The subsequent procedure depends on circumstances. Some acetals, such as benzophenone dimethyl acetal, may crystallise out. More generally, the product is fractionated under reduced pressure and the distillate poured into 30% aqueous potassium hydroxide (500 c.c. for every g.-mol. of orthosilicic ester) and the mixture shaken to hydrolyse the silicon esters present (if higher silicon esters are present, the mixture should be boiled). The layer of acetal which is now free from silicon is separated, dried in contact with potassium carbonate, and distilled.

(g) *Formation of Diacyl Derivatives.*

It has been known for some time that di-esters of the type $R\cdot CH(OAc)_2$ could be obtained either by treating alkylidene dihalides with salts of the appropriate acids (Wicke, *Annalen*, 1857, **102**, 366; Engelhardt, *J. pr. Chem.*, 1857, [i], **72**, 326; compare Butleroff, *Annalen*, 1858, **107**, 111; Auwers and H. Burrows, *Ber.*, 1899, **32**, 3034), or by heating aldehydes with suitable acid anhydrides (Geuther, *Annalen*, 1858, **106**, 249; Guthrie and Kolbe, *ibid.*, 1859, **109**, 299; Franchimont, *Rec. trav. chim.*, 1882, **1**, 248).

Both these methods of preparation indicate that these substances can be considered as the esters of the ortho-form of the aldehyde, $R\cdot CH(OH)_2$.

A convenient method of preparation is to allow the aldehyde to react with the appropriate acid anhydride in presence of a catalyst. For this purpose sulphuric acid in small amount has been employed very successfully (Skraup, *Monatsh.*, 1898, **19**, 458; Wegscheider and Späth, *ibid.*, 1909, **30**, 840; Wohl and Maag, *Ber.*, 1910, **43**, 3292).

Preparation of Ethylidene Diacetate—Acetaldehyde (16 g.) and acetic anhydride (80 c.c.) are mixed and a trace of concentrated sulphuric acid is added by means of a glass rod. The reaction mixture becomes warm, and it is advisable to cool it. When the initial reaction has moderated, 2 drops of sulphuric acid are added. After 12 hours at room temperature it is poured into water, the oil separated by ether, washed with dilute sodium carbonate solution, dried, and distilled, b. p. 168°—yield 19 g. (Wegscheider and Späth, *loc. cit.*).

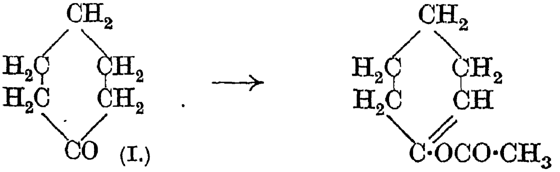
Preparation of Benzylidene Diacetate.—1 Drop of concentrated sulphuric acid is added to a solution of 1 g. of benzaldehyde in 5 c.c. of acetic anhydride. After 15 minutes it is shaken with about 25—30 c.c. of water. The diacetate separates as an oil which solidifies on keeping, m. p. 43°—yield almost theoretical.

o- and *p*-Nitrobenzaldehydes yield acetates by a similar process. Salicylaldehyde yields the diacetate of *o*-acetoxysalicylaldehyde in this manner (Wegscheider and Späth, *loc. cit.*).

There appears to be no record of the formation of diacyl derivatives of ketones by any of the methods given above (compare Wegscheider, *loc. cit.*).

(h) *Enolisation.*

The grouping $-CH_2\cdot CO-$ has a tendency to change into the enolic form—$CH\colon C(OH)$—under suitable conditions. With the simple aldehydes and ketones, the evidence for this is dependent on their conversion into enolic derivatives. Thus *cyclo*hexanone (I) heated for a long time with acetic anhydride and sodium acetate is converted into *cyclo*hexenol acetate (II). Other cyclic ketones (Mannich, *Ber.*, 1906, **39**, 1594) and some aliphatic aldehydes and ketones behave similarly (Semmler, *Ber.*, 1909, **42**, 584, 1161; Hâncu, *ibid.*, 1909, **42**, 1052). It is not improbable, however, that the formation of enol acetates from aldehydes is not preceded by enolisation, but is dependent on the elimination of a molecule of acetic acid from the diacetate. Some support for this is derived from the observations of Claisen (*Ber.*, 1896, **29**, 1006; 1898, **31**, 1019; compare 1907, **40**, 3908) that acetals, on treatment with acetyl chloride and pyridine or with quinoline and phosphorus pentoxide, eliminate the elements of alcohol to furnish ethers of the enolic forms of the aldehydes or ketones.



(I.) (II.)

On the other hand, there is evidence from the reaction with bromine and iodine that acetone and some of its homologues can react in the enolic form (Lapworth, *J.*, 1908, **93**, 2189; Dawson and Leslie, *ibid.*, 1909, **95**, 1860; Dawson and Wheatley, *ibid.*, 1910, **97**, 2048; Dawson and Powis, *ibid.*, 1912, **101**, 1503).

It has not yet been possible to isolate the enols of the simpler ketones or to show that they are present in a detectable amount in ordinary specimens (compare K. H. Meyer, *Ber.*, 1912, **45**, 2852).

It has been shown satisfactorily that liquid β-ketonic esters and 1 : 3-diketones, containing the grouping $-CO\cdot CH_2\cdot CO-$, are mixtures of enolic and keto forms, and from some of these both forms have been isolated in a pure condition. The existence of the enol is shown by coloration with ferric chloride and by the formation of characteristic copper salts (see p. 102). The amount of enol can be estimated by K. H. Meyer's method of titration with bromine (see p. 105) or by determination of the refractive index if the constants of both forms are known. The point of equilibrium between the two forms is apparently dependent on the external conditions of temperature and on the solvent (K. H. Meyer, *Annalen*, 1911, **380**, 212; *Ber.*, 1912, **45**, 2843).

The following table illustrates the effect of the solvent, and gives the percentage of enol in a 3—5 % solution.

Solvent.	Temperature.	Aceto-acetic Ester.	Benzoyl Acetic Ester.	Acetyl Acetone.
	—	7·4	16·7	76
Water	0°	0·4	0·8	19
Formic acid	20	1·1	2·8	48
Acetic acid	20	5·7	14	74
Methyl alcohol	0	6·9	13·4	72
Chloroform	20	8·2	15·3	79
Ethyl alcohol	0	12·7	26	84
Benzene	20	18	31	85
Hexane	20	48	69	92
Pyridine	—	56	—	—

Values for the enol content of equilibrium mixtures of other β-ketonic esters and 1 : 3-diketones have been given by K. H. Meyer (*loc. cit.*) and by Dieckmann (*Ber.*, 1922, **55**, 2470).

When the substance is crystalline, the pure substance is either entirely enol or entirely keto, but by solution or fusion it is converted more or less rapidly into the equilibrium mixture. Some substances are known both in enolic and ketonic states. Thus the keto-form of acetoacetic ester has been isolated by taking advantage of its sparing solubility in solvents at — 78°, and it can be crystallised at low temperatures. The enolic forms of benzoyl acetic ester and acetyl acetone have been obtained by a similar process (Knorr and Hermann Fischer, *Ber.*, 1911, **44**, 2771). Enolic acetoacetic ester has been obtained by treating its sodium salt with dry hydrogen chloride at — 78° in presence of light petroleum (Knorr, Rothe, and Averbeck, *Ber.*, 1911, **44**, 1138; Knorr, *ibid.*, p. 2767). An interesting process of obtaining pure enol and keto-forms of acetoacetic ester has been described by K. H. Meyer and Schoeller (*Ber.*, 1920, **53**, 1410) and by K. H. Meyer and Hopff (*ibid.*, 1921, **54**, 579). They find that the ester distilled under reduced pressure from glass flasks gives a distillate rich in enol and a residue containing a high proportion of keto-form. The distillate fractionated immediately from a fused quartz apparatus gives the pure enol. The enolic form of acetyl acetone has been similarly obtained. Fractional distillation of acetoacetic ester from quartz vessels—which contain no catalyst to accelerate the attainment of equilibrium—gives a residue of the pure keto-ester.

(2) *Special Reactions of Aldehydes.*

(a) *Oxidation.*—The aldehydes are converted by oxidation into carboxylic acids containing the same number of carbon atoms as the original aldehyde

$$R\cdot CHO + O \longrightarrow R\cdot CO_2H$$

For this purpose a large variety of oxidising agents are available: permanganate, hydrogen peroxide, peracids, silver oxide, nitric acid, hypochlorite, and oxygen.

A number of aldehydes, particularly benzaldehyde and its homologues, are oxidised to the corresponding acids by contact with air. The reaction depends apparently on the intermediate formation of peracid, the formation of benzoic acid from benzaldehyde being represented by the scheme (Baeyer and Villiger, *Ber.*, 1900, **33**, 1581)

$$Ph\cdot CHO + O_2 \longrightarrow Ph\cdot CO\cdot O\cdot OH \xrightarrow{PhCHO} 2Ph\cdot CO_2H$$

By effecting the aerial oxidation of benzaldehyde in presence of acetic anhydride, it is possible to check the oxidation at the peracid stage, the perbenzoic acid being converted into acetyl benzoyl peroxide.

Preparation of Acetyl Benzoyl Peroxide, $Ph\cdot CO\cdot O\cdot O\cdot CO\cdot CH_3$.—A mixture of benzaldehyde (8 g.), acetic anhydride (16 g.), and sand (200 g.) is spread on porcelain dishes in a thin layer and kept in diffused light for 4 days. The mixture is then extracted with ether. The ethereal solution is washed with sodium carbonate solution, dried, and then evaporated. Acetyl benzoyl peroxide remains as a neutral oil, which solidifies. It crystallises from light petroleum, m. p. 37—39° (Nef, *Annalen,* 1897, **298**, 284).

The use of peracids as general reagents for the oxidation of saturated aldehydes has been suggested by D'Ans and Kneip (*Ber.*, 1915, **48**, 1143). Using peracetic acid as the oxidising agent, they converted benzaldehyde, anisaldehyde, and œnanthaldehyde almost quantitatively into the corresponding acids. *p*-Hydroxybenzaldehyde yielded quinol, and this would appear to be an example of Dakin's reaction (P., 1909, **25**, 194) whereby *o*- and *p*-phenolic aldehydes are converted into *o*- and *p*-dihydric phenols by the action of hydrogen peroxide.

The oxidation of acetaldehyde to acetic acid by molecular oxygen is of industrial importance, and requires a catalyst for efficient working. Many substances have been proposed as suitable catalysts: manganous, ferric, or nickel salts. Of these the manganous salts are stated to be very efficient.

The oxidation of saturated aliphatic aldehydes and of benzaldehyde and its alkoxy- and nitro- and halogen-substituted derivatives can be achieved smoothly by the action of cold or warm aqueous permanganate containing sodium carbonate, or by the action of an acetone solution of permanganate. Homologues of benzaldehyde are similarly oxidised, but the amount of permanganate must be carefully regulated to prevent the alkyl groups being attacked.

Nitric acid, either diluted or concentrated, has been used for this oxidation, particularly for halogen-substituted aliphatic aldehydes (Moureu, Murat, and Tampier, *Compt. rend.*, 1921, **172**, 1267) and polyhydroxy aldehydes (Kiliani, *Ber.*, 1921, **54**, 460; 1922, **55**, 75; compare *ibid.*, 1888, **21**, 3006).

Aldehydes which are broken down by the usual oxidising agents can generally be converted quite smoothly into the corresponding carboxylic acid by treatment with an aqueous suspension of silver oxide or an ammoniacal solution of silver nitrate containing some alkali. Delépine and Bonnet (*Compt. rend.*, 1909, **149**, 39) have described experimental conditions for the oxidation which give almost theoretical yields. This type of oxidation has been applied successfully not only to unsaturated aldehydes, but also to amino-aldehydes (E. Fischer, *Ber.*, 1913, **46**, 2510; Stoermer and Prall, *ibid.*, 1897, **30**, 1508).

Mercuric oxide has been used to a limited extent for the oxidation of reducing sugars to the corresponding polyhydroxy-acids (Blanchietère, *Bull. Soc. chim.*, 1923, [iv], **33**, 345). Bromine water has been used more extensively for this purpose (E. Fischer and Hirschberger, *Ber.*, 1889, **22**, 3218; E. Fischer and Herborn, *ibid.*, 1896, **29**, 1961; Will and Peters, *ibid.*, 1888, **21**, 1813; E. W. Allen and Tollens, *Annalen*, 1890, **260**, 306; Kiliani and Kleemann, *Ber.*, 1884, **17**, 1298; Kiliani, *ibid.*, 1886, **19**, 3031). Improvements in the technique have recently been described by Ling and Nanji (*J.S.C.I.*, 1922, **41**, 28).

An interesting reaction of the aldehydes is their behaviour with alkali salts of nitrohydroxylaminic acid, $Na_2N_2O_3$. The reaction is effected in alcoholic aqueous solution containing alkali, and the aldehyde is converted into the corresponding hydroxamic acid (XXIV), which by hydrolysis with dilute acid gives the carboxylic acid and hydroxylamine (Angeli and Angelico, *Gazzetta*, 1903, **33**, [ii], 239). Instead of nitrohydroxylaminic acid, benzene sulphonyl hydroxylamine, $Ph{\cdot}SO_2{\cdot}NHOH$ (Piloty, *Ber.*, 1896, **29**, 1559), and its homologues may also be employed, and are very convenient for this purpose, as they are easily prepared.

$$PhSO_2{\cdot}NHOH + R{\cdot}CHO \longrightarrow$$

$$PhSO_2H + \underset{\text{(XXIV.)}}{R{\cdot}C(OH){:}NOH} \xrightarrow{\text{hydrolysis}} R{\cdot}C(OH){:}O + NH_2OH$$

The hydroxamic acids are characterised by their copper salts, and the formation of these copper salts has been employed for the estimation of aldehydes. Although this reaction succeeds with most aldehydes, it fails with *o*-nitrobenzaldehyde and salicylaldehyde. Further information on the point can be obtained by consulting the following papers: Angeli and collaborators, *Gazzetta*, 1900, **30**, [i], 593; 1904, **34**, [i], 56; *Atti R. Accad. Lincei*, 1901, [v], **10**, [i], 249; 1908, [v], **17**, [ii], 360. Ciamician and Silber, *Ber.*, 1908, **41**, 1071).

(b) *Cannizzaro Reaction.*—It was noticed by Liebig and Wöhler (*Annalen*, 1832, **3**, 252) that benzaldehyde yielded benzoic acid by the action of potash. Benzyl alcohol was not recognised as a product of this reaction until 1853 (Cannizzaro, *Annalen*, 1853, **88**, 129). Thus a mixture of benzyl alcohol and a benzoate is formed by emulsifying benzaldehyde with concentrated aqueous potash.

$$2\text{Ph}\cdot\text{CHO} + \text{KOH} \longrightarrow \text{Ph}\cdot\text{CH}_2\text{OH} + \text{Ph}\cdot\text{CO}_2\text{K} + \text{H}_2\text{O}$$

Preparation of Benzyl Alcohol and Benzoic Acid from Benzaldehyde.—Benzaldehyde (25 g.) is shaken in a stoppered flask with a solution of 22 g. of potassium hydroxide in 15 c.c. of water till a permanent emulsion is formed. The mixture is kept overnight, when sufficient water is added to completely dissolve the crystalline benzoate which has separated. The sparingly soluble benzyl alcohol is then extracted by shaking the mixture with several separate quantities of ether. The combined ethereal extracts are freed from small amounts of unchanged aldehyde by shaking twice with concentrated sodium bisulphite solution. The ethereal solution must then be freed from sulphurous acid by shaking with concentrated sodium carbonate solution. Afterwards it is dried in contact with anhydrous sodium sulphate and distilled. Benzyl alcohol is collected at 204—206°—yield about 8—10 g.

Acidification of the aqueous layer from the ether extraction precipitates benzoic acid, which is collected by filtration and recrystallised from hot water, m. p. 121°—yield 9—10 g.

Alkyl, alkoxy-, and halogen-substituted benzaldehydes also give this reaction. Nitrobenzaldehydes also suffer dismutation under the influence of aqueous alkali, but at the same time other reactions may occur if the alkali is too concentrated (Maier, *Ber.*, 1901, **34**, 4132). Hydroxy aldehydes apparently do not undergo the Cannizzaro reaction.

Preparation of m-*Nitrobenzyl Alcohol.*—*m*-Nitrobenzaldehyde (5 g.) is added to a solution of 2·5 g. of potassium hydroxide in 15 c.c. of water and the mixture kept overnight. The mixture is then saturated with carbon dioxide and extracted with ether. Evaporation of the ether furnishes *m*-nitrobenzyl alcohol, m. p. 27° (Becker, *Ber.*, 1882, **15**, 2090; Thorp and Wildman, *J. Amer. Chem. Soc.*, 1915, **37**, 373).

The Cannizzaro reaction is not confined to the aromatic series. Aldehydes which by virtue of their structure are unable to yield products of the aldol type undergo dismutation readily (Lieben, *Monatsh.*, 1901, **22**, 289; Neustädter, *ibid.*, 1906, **27**, 903). Formaldehyde, the simplest of these, furnishes methyl alcohol and a formate when treated with aqueous alkali. Other aldehydes behaving similarly are furfuraldehyde (Schiff, *Annalen*, 1891, **261**, 255; Wissell and Tollens, *ibid.*, 1893, **272**, 292); α-hydroxymethyl-αα-dimethylpropaldehyde (Wessely, *Monatsh.*, 1901, **22**, 66); α-methyl-α-hydroxymethyl-*n*-butaldehyde (Neustädter, *Annalen*, 1907, **351**, 295); α-hydroxy*iso*butaldehyde (Franke, *Monatsh.*, 1896, **17**, 666; 1900, **21**, 1122).

Apparently, most aldehydes are able to undergo dismutation if the conditions are suitable. Aqueous alkali favours the aldol condensation of aldehydes of the type $\text{R}\cdot\text{CH}_2\cdot\text{CHO}$, rather than the Cannizzaro reaction, but even using this reagent it has been possible to show that with acetaldehyde dismutation occurs to a small extent (Hammarsten, *Annalen*, 1920, **420**, 262). A similar observation has been made by W. H. Perkin, jun. (*Ber.*, 1882, **15**, 2803; 1883, **16**, 210), with œnanthaldehyde.

If the aldehyde has a comparatively slight tendency to aldol formation, conditions may be arranged so that the Cannizzaro reaction occurs to a considerable extent. Thus *iso*butaldehyde, which yields a mixture of *iso*butyrate, the aldol, and its dismutation products by the action of aqueous sodium hydroxide, is converted largely into *iso*butyl alcohol and *iso*butyrate by heating with aqueous baryta in a sealed tube (Lederer, *Monatsh.*, 1901, **22**, 536).

The dismutation of aliphatic aldehydes takes place readily and smoothly under the influence of suitable animal tissues, such as liver or spleen (Batelli and Stern, *Biochem. Z.*, 1910, **28**, 145; Parnas, *ibid.*, 1910, **28**, 274). Undoubtedly, the most satisfactory method for the dismutation of aliphatic aldehydes consists in treating them with aluminium or magnesium alkoxides. Under the influence of these substances acetaldehyde is converted into ethyl acetate; *iso*butaldehyde furnishes *iso*butyl *iso*butyrate; chloral yields the trichloroethyl ester of trichloroacetic acid (Tischtschenko, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 355).

$$2CH_3{\cdot}CHO \longrightarrow CH_3{\cdot}CO{\cdot}OC_2H_5.$$

Aluminium alkoxides appear to be the most effective for this reaction, and if used in xylene solution, the proportion required to complete the change in acetaldehyde is only about 3% of the weight of the aldehyde (Child and Adkins, *J. Amer. Chem. Soc.*, 1923, **45**, 3013; 1925, **47**, 798).

(c) *Acyloin Condensation.*—The best-known example of this reaction is the formation of benzoin from benzaldehyde under the influence of potassium cyanide:

$$2Ph{\cdot}CHO \qquad Ph{\cdot}CO{\cdot}CHOH{\cdot}Ph.$$

Preparation of Benzoin.—A mixture of benzaldehyde (10 g.), 25 c.c. of alcohol, and 2 g. of potassium cyanide dissolved in 5 c.c. of water is boiled on a water-bath under reflux for 1—2 hours. It is then cooled slowly, and the benzoin which separates out is collected by filtration and washed with a little ice-cold alcohol. It crystallises from alcohol as white needles, m. p. 137° (Zinin, *Annalen*, 1840, **34**, 187; Zincke, *ibid.*, 1879, **198**, 150, *footnote*).

This reaction has been applied to the preparation of acyloins from *o*- and *p*-tolylaldehydes, and halogen and alkoxy-substituted benzaldehydes (compare Buck and Ides, *J. Amer. Chem. Soc.*, 1932, **54**, 3302), and furfuraldehyde.

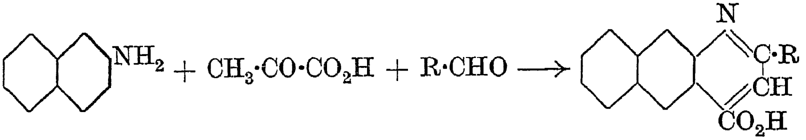
Preparation of Anisoin.—A mixture of 10 g. of anisaldehyde, 12 g. of alcohol, 8 c.c. of water, and 2 g. of potassium cyanide is heated under reflux for 2 hours. A further amount of 2 g. of potassium cyanide is then added and the heating continued for 1—2 hours.

The solution is then allowed to cool, while it is shaken vigorously. Anisoin crystallises out, is collected, washed with water, and purified by crystallisation from alcohol (Bösler, *Ber.*, 1881, **14**, 327).

Preparation of Furoin.—A mixture of furfuraldehyde (40 g.), 80 c.c. of water, and 30 g. of alcohol is heated under reflux with 4 g. of potassium cyanide for 30—40 minutes. The reaction is then rendered faintly acid with acetic acid and cooled. Furoin separates out as a crystalline mass. It is collected by filtration, washed with water, and then with aqueous methyl alcohol to remove as much as possible of the colouring matter. It is purified by crystallisation from methyl alcohol after boiling with decolorising charcoal, and finally from a mixture of toluene and alcohol, m. p. 135° (E. Fischer, *Annalen*, 1882, **211**, 218; Hartmann and Dickey, *J. Amer. Chem. Soc.*, 1933, **55**, 1228)—yield 20—30 g.

The mechanism of this reaction and the part played by the cyanide are discussed by Lapworth (*J.*, 1903, **83**, 1004); compare Nef (*Annalen*, 1897, **298**, 312).

(d) *Doebner's Reaction.*—The condensation of aldehydes with primary aromatic amines in presence of pyruvic acid to yield cinchonic acids is sometimes employed for the characterisation of aldehydes (Doebner, *Ber.*, 1894, **27**, 352; *Annalen*, 1887, **242**, 265).

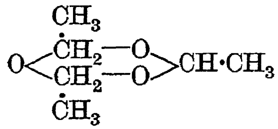


For this test, β-naphthylamine is frequently used because the alkyl naphthaquinolines obtained by heating the cinchonic acids are mostly crystalline. It should be noted that in the absence of an added aldehyde, the pyruvic acid may give sufficient acetaldehyde to yield α-methylnaphthacinchonic acid, m. p. 310°, furnishing β-naphthaquinaldine, m. p. 82°, on heating.

The following general conditions serve for the preparation of β-naphthacinchonic acids.

Pyruvic acid is mixed with a slight excess of the aldehyde in absolute alcohol and 1 mol. prop. of β-naphthylamine. After heating for several hours on the water-bath, the crude naphthacinchonic acid which separates is purified by washing with ether and crystallisation from hot alcohol. It may also be necessary to free it from neutral substances by solution in dilute ammonia before crystallisation (compare Borsche, *Ber.*, 1908, **41**, 3884).

(e) *Polymerisation.*—The aliphatic aldehydes show a marked tendency to polymerise under the influence of suitable catalysts, *e.g.*, small amounts of sulphuric acid, dry hydrogen chloride, sulphur dioxide, or zinc chloride. If one of these be added to acetaldehyde, a noticeable rise in temperature occurs—the aldehyde boils and a liquid is produced having physical properties quite distinct from acetaldehyde. The pure product has, moreover, no aldehydic reactions, since it is indifferent to Schiff's reagent, to phenylhydrazine and hydroxylamine, and to ammoniacal silver nitrate. Its molecular weight corresponds to the formula $(CH_3 \cdot CHO)_3$. This polymer of acetaldehyde, paracetaldehyde, is formulated thus:



$$O<\begin{matrix}\overset{CH_3}{\dot{C}H_2}-O \\ \underset{CH_3}{\dot{C}H_2}-O\end{matrix}>CH\cdot CH_3$$

It is reconverted into monomeric acetaldehyde by distillation with a small amount of sulphuric acid (p. 147). Apparently under the influence of a catalyst equilibrium is established between acetaldehyde and its polymer (Turbaba, *Z. phys. Chem.*, 1901, **38**, 505; Hollmann, *ibid.*, 1903, **43**, 129).

If the polymerisation of acetaldehyde is effected at low temperatures—below 0°—by dry hydrogen chloride or sulphuric acid, a solid polymer, metacetaldehyde is obtained. It is readily freed from paracetaldehyde, which is produced at the same time by filtration (Kekulé and Zincke, *Annalen*, 1872, **162**, 146). Measurements of the molecular weight of metacetaldehyde have so far yielded no concordant results, and presumably the values are vitiated by association and perhaps by dissociation also (compare Hantzsch and Oechslin, *Ber.*, 1907, **40**, 4341). Metacetaldehyde, like paracetaldehyde, displays none of the reactions of substances containing an aldehyde group. It is presumably an ether-like compound, but no definite structural formula has yet been accepted.

Under similar conditions the homologues of acetaldehyde yield a para and a meta series of polymers (see Francke and Wozelka, *Monatsh.*, 1912, **33**, 349; Francke and Hinterberger, *ibid.*, 1923, **43**, 659; Orndorff, *Amer. Chem. J.*, 1890, **12**, 353).

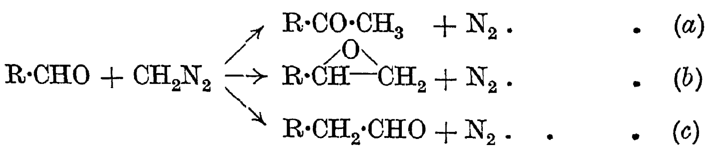
The higher homologues (from C_{11} upwards) are stated to polymerise spontaneously on keeping, but the polymerisation is accelerated by the presence of bisulphite or acid (Blaise and Guérin, *Bull. Soc. chim.*, 1903, [iii], **29**, 1202; le Sueur, *J.*, 1904, **85**, 833; 1905, **87**, 1892 *et seq.*). Hexahydrobenzaldehyde is also stated to polymerise spontaneously. A similar behaviour is observed with some of the halogen-substituted aliphatic aldehydes, but here the action is catalysed presumably by the formation of traces of halogen hydride (H. Hibbert and Hill, *J. Amer. Chem. Soc.*, 1923, **45**, 743; Grabowski, *Ber.*, 1875, **8**, 1436). Their polymerisation is, however, assisted by the presence of an added catalyst such as sulphuric acid or hydrochloric acid (compare Kolbe, *Annalen*, 1845, **54**, 183, *footnote*; Jacobsen, *Ber.*, 1875, **8**, 88; Grimaux and Adam, *Bull. Soc. chim.*, 1881, [ii], **36**, 23, 136).

Formaldehyde polymerises to yield a variety of products. Evaporation of its aqueous solution gives paraformaldehyde, an amorphous solid containing loosely combined water. Polymers are formed also by the action of sulphuric acid on aqueous solutions of formaldehyde, which are known as α-, β-, γ-, or δ-polyoxy-methylenes. Another, a crystalline form, trioxymethylene, has also been described, and is prepared by subliming any of the polyoxymethylenes into water. These polymers are represented by Staudinger as long chains of formaldehyde molecules, $\cdot O\cdot CH_2\cdot O\cdot CH_2\cdot(O\cdot CH_2)_n\cdot O\cdot CH_2\cdot$. The chemical differences observed with the different polymeric modifications are attributed to different terminal groupings. Thus α-polyoxymethylene is formulated as $OH\cdot CH_2\cdot O\cdot(CH_2)_n\cdot CH_2OH$; γ-polyoxymethylene as $CH_3O\cdot CH_2\cdot O\cdot(CH_2O\cdot)_n\cdot CH_2O\cdot CH_3$ (Staudinger, *Ber.*, 1920, **53**, 1073; Staudinger, Johner, Lüthy, and Signer, *Annalen*, 1929, **474**, 155).

Amorphous polymers can be obtained from other aldehydes. Chloral yields a solid substance under the influence of sulphuric acid. By the action of pyridine or trimethylamine upon chloral a polymeride is obtained having indefinite physical properties (V. Meyer and Dulk, *Annalen*, 1874, **171**, 76; Böeseken and Schimmel, *Rec. trav. chim.*, 1913, **32**, 112, 128). Most aliphatic dialdehydes polymerise more or less easily to glassy solids (Baeyer and Villiger, *Ber.*, 1897, **30**, 1963; Harries, *ibid.*, 1902, **35**, 1184; Harries and Tank, *ibid.*, 1908, **41**, 1705; Harries and Temme, *ibid.*, 1907, **40**, 167; Wohl and Schweitzer, *ibid.*, 1907, **39**, 894; v. Braun and Danziger, *ibid.*, 1913, **46**, 107).

(f) *Reaction with Diazomethane.* 1. *Aldehydes.*—It was first reported by Schlotterbeck (*Ber.*, 1907, **40**, 479; 1909, **42**, 2561) that aldehydes react with ethereal solutions of diazomethane to give ketones as the final product. Thus benzaldehyde gave 97% yield of acetophenone; œnanthaldehyde furnished methyl hexyl ketone in 73% yield (compare H. Meyer, *Monatsh.*, 1905, **26**, 1300). He extended the reaction (*Ber.*, 1909, **42**, 2565) to diazoacetic ester, which was found to react with aldehydes to yield β-keto-esters.

More recent investigations have shown that the general reaction of aldehydes with diazomethane is more complex, and can be represented as follows :



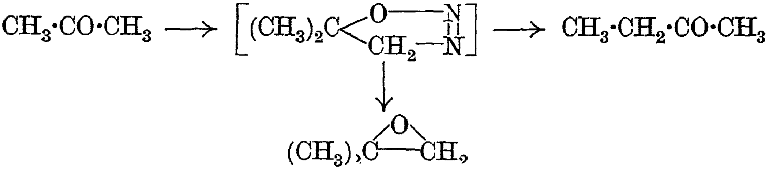
$$R\cdot CHO + CH_2N_2 \rightarrow \begin{cases} R\cdot CO\cdot CH_3 + N_2 & (a) \\ R\cdot \overset{\diagup O \diagdown}{CH-CH_2} + N_2 & (b) \\ R\cdot CH_2\cdot CHO + N_2 & (c) \end{cases}$$

(Arndt and Eistert, *Ber.*, 1928, **61**, 1118).

The formation of the higher aldehyde indicated by (*c*) usually occurs to only a small extent. The principal products are those resulting from reactions (*a*) and (*b*). The relative proportion of the products is dependent on the aldehyde used and to some extent on the presence of certain promoters. Thus the relative proportions of (*a*), (*b*), and (*c*) obtained from *p*-nitrobenzaldehyde are approximately 9 : 13 : 1, while if methyl alcohol is present the proportions are 4·5 : 6 : 1 (Arndt, Eistert, and Ender, *Ber.*, 1929, **62**, 44).

This reaction has been applied to a number of aldehydes such as chloral, dibromopropionaldehyde, *o*-nitrobenzaldehyde.

2. *Ketones.*—Perfectly dry acetone is indifferent to diazomethane. If water is present, however, reaction occurs readily with the formation of an ethylene oxide as the principal product, together with small amounts of diethyl ketone and methyl ethyl ketone (Meerwein and Burneleit, *Ber.*, 1928, **61**, 1840). Ethyl alcohol, a dilute aqueous solution of lithium chloride, or formamide may be used instead of water for catalysing the reaction (Meerwein, Bersin, and Burneleit, *Ber.*, 1929, **62**, 999). Its mechanism according to Meerwein and his co-workers is as follows :



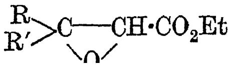
It is interesting to note that the explanation of the reaction of diazomethane with acyl chlorides and aldehydes advanced by Bradley and Robinson (*J.*, 1928, 1314) to cover the facts of the reaction as then known can be applied with little modification to account for the more recently discovered facts.

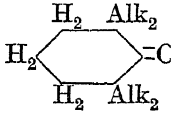
(3) *Special Reactions of Ketones.*

(a) *Alkylation of Ketones.*—It was found by Nef (*Annalen*, 1900, **310**, 316) that acetophenone or acetone when heated at 100° with powdered potash and an alkyl iodide underwent alkylation at the carbon atom adjacent to the carbonyl group. The technique was subsequently improved by Claisen, who used an ethereal solution of the ketone and substituted sodamide for potash (*Ber.*, 1905, **38**, 697). If chloroacetic ester be used instead of alkyl halides in this reaction, glycide esters result (XXVII) (Claisen, *Ber.*, 1905, **38**, 702). The scope of this reaction has since been explored by Haller and his co-workers. It has been employed for the introduction of alkyl groups into cyclic ketones such as *cyclo*hexanone and its homologues, *cyclo*pentanone and methyl*cyclo*pentanone; into such aliphatic ketones as diethyl ketone and di*iso*propyl ketone; into acetophenone and its homologues, and into benzoyl*cyclo*propane (Haller, *Compt. rend.*, 1913, **156**, 737, 1199; **157**, 179; Haller and E. Bauer, *Ann. Chim.*, 1913, [viii], **29**, 313; Haller and E. Bauer, *Compt. rend.*, 1914, **158**, 825; Haller and Cornubert, *ibid.*, pp. 298, 1616; Haller and Benoist, *Ann. Chim.*, 1922, [ix], **17**, 25). The result of the reaction is to replace one or more of the hydrogens attached to the carbon atoms adjacent to the carbonyl group by alkyl groups. Acetophenone yields as the final product of methylation, phenyl *tert.*-butyl ketone (XXV). Phenyl undecyl ketone gives (XXVI). *cyclo*Hexanones give alkyl*cyclo*hexanones of the type (XXVIII), and by using methyl iodide it is also possible to introduce alkyl groups into the *para* position with respect to the carbonyl group. The substitution can also be regulated so that fewer alkyl groups are introduced.

(XXV.) $Ph{\cdot}CO{\cdot}CMe_3$ $Ph{\cdot}CO{\cdot}CMe_2{\cdot}(CH_2)_9{\cdot}CH_3$ (XXVI.)

(XXVII.)





(XXVIII.)

For the application of this reaction to the synthesis of substituted tetrahydropyridines see Haller and Ramart-Lucas (*Ann. Chim.*, 1917, [ix], 8, 5).

(b) *Fission of Ketones.*—Ketones having the carbonyl group between two tertiary carbon atoms—as in $(Me)_3C{\cdot}CO{\cdot}C(Me)_3$ or $Ph{\cdot}CO{\cdot}CMe_3$—are split into a mixture of hydrocarbon and amide by boiling with sodamide in benzene or toluene. Thus $Ph{\cdot}CO{\cdot}CMe_3$ yields benzene and $Me_3C{\cdot}CO{\cdot}NH_2$; $Me_3C{\cdot}CO{\cdot}CMe_3$ gives $Me_3C{\cdot}CONH_2$ and Me_3CH. Unsymmetrical aliphatic ketones undergo fission in two directions, yielding in general a mixture of two amides and two hydrocarbons (Haller and Bauer, *Compt. rend.*, 1909, **148**, 127; 1909, **149**, 5). Under slightly different conditions the aromatic ketones, benzophenone, phenyl *p*-tolyl ketone, or phenyl *p*-anisyl ketone, yield a mixture of benzamide and the appropriate amide. Fluorenone, on the other hand, is decomposed directly to give the amide of diphenyl-*o*-carboxylic acid (Haller and Bauer, *Compt. rend.*, 1908, **147**, 824).

An interesting type of reaction of the aryl alkyl ketones was discovered by Willgerodt. Acetophenone heated at 200—220° with yellow ammonium sulphide yields a mixture of the amide and the ammonium salt of phenylacetic acid. Phenyl ethyl ketone behaves similarly, and so do its homologues, although the yield becomes smaller with increasing length of the alkyl group, until with C_5 and C_6 alkyl phenyl ketones the yield of amide and ammonium salt is very small. The best yields are obtained with the methyl aryl ketones, and may reach 50%.

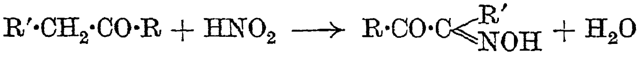
A number of other products are formed in this reaction. Reduction of the carbonyl group occurs to some extent, and with acetophenone appreciable amounts of 2 : 4- and 2 : 5-diphenylthiophenes are formed (Willgerodt and Scholtz, *J. pr. Chem.*, 1910, [ii], **81**, 384; Willgerodt and Hambrecht, *ibid.*, 1910, [ii], **81**, 74; Willgerodt and Merk, *ibid.*, 1909, [ii], **80**, 192; Willgerodt, *ibid.*, 1909, [ii], **80**, 183). With phenyl alkyl ketones containing long side-chains some fission to salts of aliphatic acids has also been observed.

(c) *Internal Condensation of Alkyl Benzophenones.*—Homologues of benzophenone containing a methyl group in the ortho-position to carbonyl undergo a curious change on heating under reflux. Alkyl-substituted anthracenes are formed (Elbs and Larsen, *Ber.*, 1884, **17**, 2847; Elbs, *J. pr. Chem.*, 1886, [ii], **33**, 185; 1887, **35**, 465; Elbs and Olberg, *Ber.*, 1886, **19**, 408; Morgan and Coulson, *J.*, 1929, 2203).

tion of 2 : 7-Dimethylanthracene.—*p*-Tolyl 4-*m*-xylyl ketone is boiled under reflux for 6 hours. On cooling, a thick crystalline precipitate of 2 : 7-dimethylanthracene separates, and is freed from unchanged ketone by washing with ether. Further amounts of dimethylanthracene are obtained by subjecting the recovered ketone to further treatment.

The crude 2 : 7-dimethylanthracene is purified by sublimation and crystallisation from carbon disulphide and glacial acetic acid. It is obtained as rhombic flakes, m. p. 241°, having a purple fluorescence (Morgan and Coulson, *loc. cit.*).

(*d*) *Formation of* iso*Nitroso Ketones.*—Submitted to the action of nitrous acid, ketones of the general formula $RCH_2 \cdot CO \cdot R'$ yield an *iso*nitroso-derivative as the first product



$$R' \cdot CH_2 \cdot CO \cdot R + HNO_2 \longrightarrow R \cdot CO \cdot C \lessgtr^{R'}_{NOH} + H_2O$$

The nitrous acid for this purpose is best generated by the use of amyl nitrite and hydrochloric acid (Claisen, *Ber.*, 1887, **20**, 252; Claisen and Manasse, *ibid.*, 1889, **22**, 526). The action of nitrous fumes on the ketone also results in the formation of an *iso*nitroso-compound, but the reaction is more difficult to regulate, and considerable proportions of other products are generally obtained (Sandmeyer, *Ber.*, 1887, **20**, 639; Behrend and Tryller, *Annalen*, 1894, **283**, 244).

*iso*Nitroso-compounds also result by reaction of a suitable ketone with an alkyl nitrite in alcoholic solution in presence of sodium ethoxide (Claisen, *Ber.*, 1887, **20**, 655; Claisen and Manasse, *ibid.*, p. 2194; 1889, **22**, 526, 530; *Annalen*, 1892, **273**, 71).

Preparation of iso*Nitrosoethyl Methyl Ketone.*—Amyl nitrite (1 l.) is added, over a period of 1 hour, to a mechanically stirred mixture of 850 c.c. of methyl ethyl ketone and 30 c.c. of concentrated hydrochloric acid. The temperature of the reaction mixture must be kept below 50° throughout the whole operation.

When all the nitrite has been added, 800 g. of crushed ice are added with 800 g. of 33% sodium hydroxide, and the whole mixture is shaken vigorously for an hour. The amyl alcohol which has been liberated during this operation is removed by three or four extractions with ether. The alkaline aqueous solution is acidified by the addition of dilute sulphuric acid, the temperature being kept below 10° by the addition of ice.

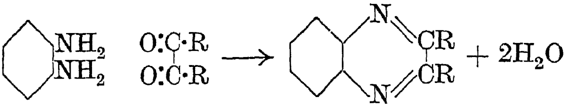
A crystalline paste of the *iso*nitroso-compound and sodium sulphate results. It is washed with a little water and then melted. The crude product is thus obtained as a crystalline cake after cooling, which can be separated from the inorganic salts (Diels and Jost, *Ber.*, 1902, **35**, 3292).

(4) *Special Reactions of Dicarbonyl Compounds.*

The most important types of these compounds are 1 : 2-diketones with the grouping $R \cdot CO \cdot CO \cdot R$; 1 : 3-diketones formulated as $R \cdot CO \cdot CH_2 \cdot CO \cdot R$; 1 : 4-diketones of the general formula $R \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO \cdot R$. Some 1 : 5- and 1 : 6-diketones are also known. In the following paragraphs the more outstanding reactions of the different types of dicarbonyl compounds are reviewed.

(a) 1 : 2-*Diketones*.—These behave normally towards hydroxylamine and semicarbazide yielding mono- and di-oximes and semicarbazones (Posner, *Ber.*, 1901, **34**, 3973). With phenylhydrazine, dihydrazones or osazones are formed.

A characteristic reaction is the formation of quinoxalines by condensation with 1 : 2-diamines. When this reaction is used for the characterisation of 1 : 2-diketones, a solution of the substance in alcohol or acetic acid is warmed with the equivalent amount of *o*-phenylenediamine or tolylene-*o*-diamine (Hinsberg, *Annalen*, 1886, **237**, 327) (see p. 294).

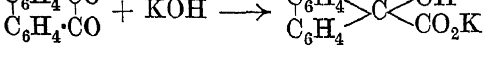


Treatment of benzil with aqueous or aqueous alcoholic potash results in the formation of a salt of benzilic acid (I) (Liebig, *Annalen*, 1838, **25**, 27; Zinin, *ibid.*, 1839, **31**, 329).

$$Ph{\cdot}CO{\cdot}CO{\cdot}Ph + KOH \longrightarrow Ph_2C(OH){\cdot}CO_2K \text{ (I).}$$

Preparation of Benzilic Acid.—Benzil (35 g.) is added to a solution of 35 g. of potassium hydroxide in a mixture of 70 c.c. of water and 70 c.c. of alcohol. An intensely dark blue solution is obtained. It is heated under reflux for 10 minutes and then transferred to a dish and kept over-night. The crystalline deposit of potassium benzilate which has formed is collected by filtration, washed with a little alcohol, and dissolved in 300 c.c. of water. Benzilic acid is precipitated by the gradual addition of concentrated hydrochloric acid. It is advisable to filter off the sticky brown precipitate which is formed by adding the first few drops of acid. The subsequent addition of acid to the filtrate gives a very pale precipitate, which is collected by filtration, washed with water, dried on porous earthenware, and finally crystallised from benzene, m. p. 150°—yield 27—30 g. (Adams and Marvel, *Organic Syntheses*, 1921, **1**, 29).

This reaction, usually referred to as the benzilic acid rearrangement, is given by a number of alkyl- and alkoxy-derivatives of benzil (Bösler, *Ber.*, 1881, **14**, 326; Gattermann, *Annalen*, 1906, **347**, 364). Phenanthraquinone under somewhat similar conditions furnishes 9-hydroxyfluorene 9-carboxylic acid (II) (Baeyer and Friedländer, *Ber.*, 1877, **10**, 125; Friedländer, *ibid.*, p. 534). Some bromo- and nitro-derivatives of phenanthraquinone behave similarly (J. Schmidt and K. Bauer, *Ber.*, 1905, **38**, 3730; Schmidt and Söll, *ibid.*, 1908, **41**, 3691).

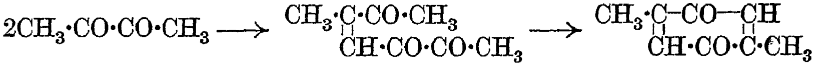


$$\begin{array}{l}C_6H_4{\cdot}CO\\ |\qquad\ \ |\\ C_6H_4{\cdot}CO\end{array} + KOH \longrightarrow \begin{array}{l}C_6H_4\\ |\\ C_6H_4\end{array}\!\!>C<\!\begin{array}{l}OH\\ CO_2K\end{array}$$

(II.)

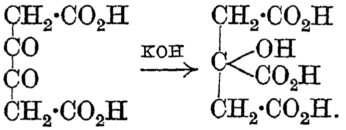
Preparation of 9-Hydroxyfluorene-9-carboxylic Acid.—Phenanthraquinone (40 g.) is heated on a water-bath with 1 litre of 2-*N*-sodium hydroxide for 1½ hours. The excess of sodium hydroxide is neutralised exactly, the tarry matter filtered off, and the filtrate acidified. The almost pure acid is precipitated. It separates from hot water in a hydrated form with $\frac{1}{2}H_2O$ of crystallisation, which is lost by drying at 105°. The anhydrous acid melts at 166° (Staudinger, *Ber.*, 1906, **39**, 3062).

The benzilic acid change occurs less frequently in the aliphatic series owing to the readiness with which condensations of the aldol type occur. Thus diacetyl and its immediate homologues yield *p*-quinones as the final product of the action of alkali (v. Pechmann, *Ber.*, 1888, **21**, 1411).



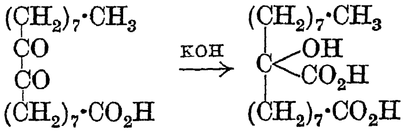
$$2CH_3\cdot CO\cdot CO\cdot CH_3 \longrightarrow \begin{array}{l} CH_3\cdot C\cdot CO\cdot CH_3 \\ \quad\; CH\cdot CO\cdot CO\cdot CH_3 \end{array} \longrightarrow \begin{array}{l} CH_3\cdot C{-}CO{-}CH \\ \quad\; CH\cdot CO\cdot C\cdot CH_3 \end{array}$$

Nevertheless, there are recorded examples of the benzilic acid rearrangement of aliphatic substances. Thus ketipinic acid (III) yields citric acid on boiling with aqueous potassium hydroxide (Franzen and F. Schmitt, *Ber.*, 1925, **58**, 222).



$$\begin{array}{l} CH_2\cdot CO_2H \\ CO \\ CO \\ CH_2\cdot CO_2H \end{array} \xrightarrow{KOH} \begin{array}{l} CH_2\cdot CO_2H \\ C{<}^{OH}_{CO_2H} \\ CH_2\cdot CO_2H. \end{array}$$

(III.)

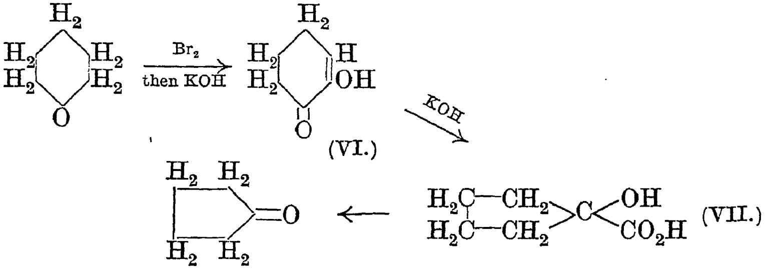


$$\begin{array}{l} (CH_2)_7\cdot CH_3 \\ CO \\ CO \\ (CH_2)_7\cdot CO_2H \end{array} \xrightarrow{KOH} \begin{array}{l} (CH_2)_7\cdot CH_3 \\ C{<}^{OH}_{CO_2H} \\ (CH_2)_7\cdot CO_2H \end{array}$$

(IV.) (V.)

Diketostearic acid (IV) is converted into α-hydroxy-α-octylsebacic acid (V) by heating with potassium hydroxide at 160° (Nicolet and Jurist, *J. Amer. Chem. Soc.*, 1922, **44**, 1136).

An interesting application of the benzilic acid change is the conversion of *cyclo*hexane derivatives into derivatives of *cyclo*pentane. Thus 1 : 2-*cyclo*hexadione (VI) yields *cyclo*pentane 1-hydroxy-1-carboxylic acid (VII) by the action of aqueous potassium hydroxide. In this reaction the diketone need not be isolated. It is an intermediate product of the action of alkali on dibromo*cyclo*hexanone.

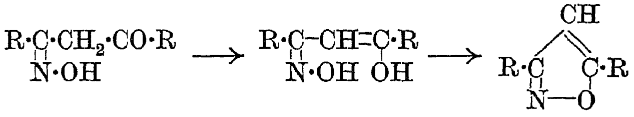


(VI.) (VII.)

As the *cyclo*pentanol carboxylic acid loses the elements of formic acid by treatment with sulphuric acid and lead peroxide to furnish *cyclo*pentanone, the reaction is an important one. It has been used for the preparation of a number of alkyl-substituted *cyclo*pentanones (Wallach, *Annalen*, 1916, **414**, 296; 1924, **437**, 148).

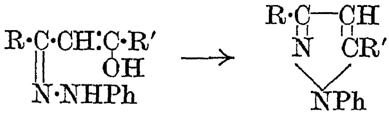
(b) 1 : 3-*Diketones.*—This class of compound includes acetyl acetone, and benzoyl acetone, $\mathrm{Ph{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3}$. The keto-enol tautomerism and the behaviour on alkylation have been referred to in previous sections (pp. 103, 157).

One of the outstanding reactions of these compounds is the ease with which they yield cyclic compounds by the action of hydroxylamine or of hydrazines. With hydroxylamine, *iso*oxazoles (VIII) result, presumably through the intermediate formation of a monoxime, which in its enolic form splits off water (Claisen, *Ber.*, 1891, **24**, 3900; Dunstan and Dymond, *J.*, 1891, **59**, 428).


(VIII.)

Preparation of 3 : 5-*Dimethyl*iso*oxazole.*—Hydroxylamine sulphate (45 g.) and potassium carbonate (39 g.) are added successively to a solution of 50 g. of acetyl acetone in 800 c.c. of water. The mixture is heated under reflux for about 2½ hours. The supernatant oil is then removed and the aqueous layer extracted with ether. After drying, the combined oil and ether extracts are fractionated. Dimethyl*iso*oxazole is collected at 140—142° as a colourless liquid (Combes, *Ann. Chim. Phys.*, 1887, [vi], **12**, 215; Morgan and Burgess, *J.*, 1921, **119**, 699).

With phenylhydrazine an analogous condensation occurs with the formation of a pyrazole (IX) (Knorr, *Annalen*, 1887, **238**, 139).

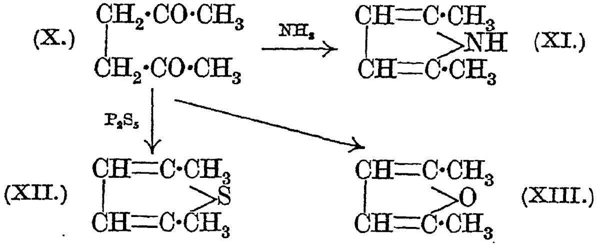

(IX.)

Semicarbazide appears to react in a similar manner (Posner, *Ber.*, 1901, **34**, 3982).

1 : 3-Diketones have found application in the synthesis of some benzopyrylium salts. Di- and tri-hydric phenols such as resorcinol, orcinol, pyrogallol, and phloroglucinol condense with acetyl acetone, benzoyl acetone or other 1 : 3-diketones under the influence of dry hydrogen chloride to furnish benzopyrylium salts (Bülow and H. Wagner, *Ber.*, 1901, **34**, 1189, 1786; Bülow and v. Sicherer, *ibid.*, p. 2368; Bülow and Grotowski, *ibid.*, 1902, **35**, 1519; Bülow and Deiglmayr, *ibid.*, 1904, **37**, 4528; Bülow and Deseniss, *ibid.*, 1906, **39**, 3664).

(c) 1 : 4-*Diketones.*—The behaviour of 1 : 4-diketones towards hydroxylamine, and, in general, reagents for the carbonyl group, appears to be normal (Posner, *loc. cit.*; compare, however, T. Gray, *J.*, 1901, **79**, 683).

These ketones exhibit a strong tendency towards the formation of cyclic compounds. With ammonia and primary and secondary amines, derivatives of pyrrole are formed (Knorr, *Ber.*, 1885, **18**, 299; 1886, **19**, 46; C. Paal, *ibid.*, 1885, **18**, 367, 2251; Lederer and Paal, *ibid.*, p. 2591). Thus acetonyl acetone (X), heated at 150° with alcoholic ammonia, yields dimethylpyrrole (XI).



Acetonylacetophenone behaves similarly, as do 1 : 4-diketonic esters such as acetophenone acetoacetic ester,

$$Ph·CO·CH_2·CH_2·CO·CH_2·CO_2Et,$$

and diacetylsuccinic ester. The latter ester reacts smoothly merely by treating it with concentrated ammonia. The reaction with this ester can be accomplished by warming with a suitable amine in an excess of acetic acid. This method has been suggested for the detection of 1 : 4-diketones. The procedure is as follows.

To a small amount of the substance dissolved in acetic acid is added a solution of ammonia in an excess of acetic acid. The mixture is boiled for ½ minute, then acidified with dilute sulphuric acid and again boiled. A pine splinter moistened with hydrochloric held in the vapour assumes a red colour due to the liberation of a pyrrole, if the original substance is a 1 : 4-diketone.

These diketones furnish thiophene derivatives (XII) by treatment with phosphorus pentasulphide, while dehydration leads to derivatives of furane (XIII) (Paal, *loc. cit.*; Paal and Lederer, *loc. cit.*).

(5) *Hydroxyaldehydes and Ketones. Carbohydrates.*

This group includes benzoin (I), acetoin (II), acetyl carbinol (III), glycollaldehyde (IV), aldol (V), as well polyhydroxyaldehydes and ketones such as glyceraldehyde (VI), dihydroxyacetone (VII) and the reducing sugars.

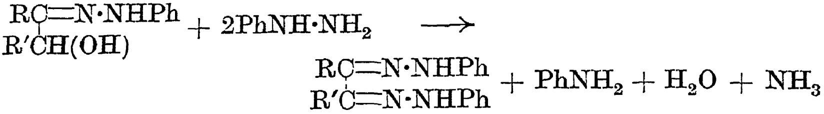
$Ph·CO·CH(OH)·Ph$ (I.) $CH_3·CO·CH(OH)·CH_3$ (II.) $CH_3·CO·CH_2(OH)$ (III.)

$CH_2(OH)·CHO$ (IV.) $CH_3·CH(OH)·CH_2·CHO$ (V.)

$CH_2(OH)·CH(OH)·CHO$ (VI.) $CH_2(OH)·CO·CH_2(OH)$ (VII.)

In these compounds the presence of the carbonyl group can be recognised by its reduction to >CH(OH) and by the formation of oximes, semicarbazones, and phenylhydrazones. Those hydroxyaldehydes and ketones which contain a primary or secondary hydroxyl group can be converted under suitable conditions to dicarbonyl compounds.

(a) *α-Hydroxyaldehydes and Ketones.*—Those having a primary or secondary hydroxyl group are converted by the action of an excess of phenylhydrazine into osazones, the normal monophenylhydrazone, which is first formed, being oxidised by the excess of phenylhydrazine to a ketohydrazone, which then yields the osazone.



$$\begin{array}{l}\mathrm{RC{=}N\cdot NHPh}\\ \mathrm{R'CH(OH)}\end{array} + \mathrm{2PhNH\cdot NH_2} \longrightarrow \begin{array}{l}\mathrm{RC{=}N\cdot NHPh}\\ \mathrm{R'C{=}N\cdot NHPh}\end{array} + \mathrm{PhNH_2} + \mathrm{H_2O} + \mathrm{NH_3}$$

This behaviour appears to be a general one. It is also given by polyhydroxyaldehydes and reducing sugars. The reaction is frequently used for the diagnosis and identification of α-hydroxy-compounds.

This reaction is an example of the ease with which α-hydroxy-carbonyl compounds undergo oxidation. Thus they are oxidised by Fehling's solution with the precipitation of cuprous oxide. Presumably, the corresponding 1 : 2-dicarbonyl compound is formed, but with aliphatic compounds further reactions occur so rapidly that the method is not practicable for the preparation of aliphatic 1 : 2-diketones (compare Nef, *Annalen,* 1904, **335**, 269). It succeeds, however, with benzoin and its analogues. Indeed, the oxidation of benzoin to the corresponding diketone, benzil, can be effected under a variety of conditions, which are inapplicable to purely aliphatic α-hydroxyaldehydes and ketones. Thus among the oxidising agents which have been used for this purpose are chlorine (Laurent, *Annalen,* 1836, **17**, 91), nitric acid (Zinin, *ibid.*, 1840, **34**, 188), aerial oxidation in presence of aqueous alkali (Klinger, *Ber.*, 1886, **19**, 1868; E. Fischer, *Annalen,* 1882, **211**, 221; Biltz and Wienands, *ibid.*, 1899, **308**, 8), chromic acid in acetic acid solution (Widman, *Ber.*, 1881, **14**, 610), aqueous alkaline permanganate (Irvine and Moodie, *J.*, 1907, **91**, 544). It should be noted, however, that few of these methods are of general application, except Fehling's solution or copper sulphate in pyridine. Examples of these oxidations are here described.

Preparation of Benzil.—A mixture of benzoin (10 g.) and nitric acid (*d* 1·4, 17 c.c.) is heated on a water-bath in a flask fitted with an air condenser. After 2 hours the contents of the flask are poured into water. The yellow solid thus obtained is collected by filtration, washed with water, and crystallised from alcohol, m. p. 95°—yield 6—8 g. (Zinin, *loc. cit.*).

Preparation of Anisil (4 : 4′*-Dimethoxybenzil*) (1).—Fehling's solution is added to a solution of anisoin (10 g.) in 50 c.c. of boiling 70% alcohol till the solution remains permanently blue. An equal volume of water is then added, and the precipitate of cuprous oxide and anisil is collected by filtration and washed with water. Anisil is extracted from the dried precipitate with benzene. After concentrating the extract by distillation, anisil separates as needles, m. p. 133°—yield almost quantitative (Bösler, *Ber.*, 1881, **14**, 327; Biltz and Wienands, *Annalen,* 1899, **308**, 8).

Preparation of Anisil (2).—Anisoin (1 g.) is heated on a water-bath with 70 g. of 5% aqueous potassium hydroxide while air is drawn through the mixture. The anisoin melts to an oil, which gradually disappears, while anisil is gradually deposited on the sides of the flask as a crust of yellow crystals—yield 80%.

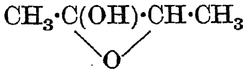
The aqueous solution contains some anisilic acid which can be precipitated by the addition of mineral acid (Biltz and Wienands, *loc. cit.*).

Preparation of Furil.—A mixture of 158 g. of crystalline copper sulphate, 210 g. of pyridine, and 90 g. of water is stirred mechanically and heated till it is homogeneous. Furoin (57 g.) is then added and the mixture stirred and heated for 2 hours. It is then poured into 1 l. of water and filtered. The black precipitate is washed with water till the washings are colourless, when it is extracted with 500 c.c. of cold methyl alcohol. Furil is isolated from the extract and purified by crystallisation from methyl alcohol—yellow needles, m. p. 165—166°, yield 36 g. (Hartmann and Dickey, *J. Amer. Chem. Soc.*, 1933, **55**, 1228).

The conversion of the aliphatic α-hydroxy-ketones into the corresponding diketones appears to be most conveniently effected by passing the vaporised hydroxy-ketone over reduced copper at 250—270° (Bouveault and Loquin, *Bull. Soc. chim.*, 1906, [iii], **35**, 650). Nitric acid (*d* 1·37) has also been used for this purpose (Ponzio, *J. pr. Chem.*, 1901, [ii], **63**, 364), while aerial oxidation of acetoin to diacetyl has been observed (v. Pechmann and Dahl, *Ber.*, 1890, **23**, 2421).

Glycollaldehyde and its immediate homologues are bimolecular in the crystalline state and when freshly dissolved in water. The monomeric form results on keeping the aqueous solutions (McCleland, *J.*, 1911, **99**, 1829). The crystalline forms of glyceraldehyde and dihydroxyacetone are also polymerised (Reeves, *J.*, 1927, 2483). Some of the simple α-hydroxy-ketones are similarly polymerised. Polymerisation also occurs when some α-hydroxy-ketones are treated with methyl alcoholic hydrogen chloride, methyl ethers of the dimeric forms being produced (E. Fischer, *Ber.*, 1895, **28**, 1161; Nef, *Annalen*, 1904, **335**, 257; Kling, *Bull. Soc. chim.*, 1904, [iii], **31**, 683).

It is of interest, in view of the behaviour of other hydroxy-carbonyl compounds (p. 174), to note that there is evidence that acetoin and similar α-hydroxy-ketones can react in a cyclic form. Kling (*Bull. Soc. chim.*, 1906, [iii], **35**, 209) has suggested that acetoin reacts as if it were an equilibrium mixture of the two forms (VIII) and (IX).



$$\mathrm{CH_3{\cdot}\underbrace{C(OH){\cdot}CH}_{O}{\cdot}CH_3}$$

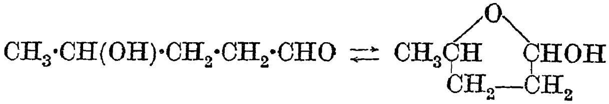
(VIII.)

$$\mathrm{CH_3{\cdot}CH(OH){\cdot}CO{\cdot}CH_3}$$

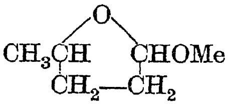
(IX.)

(b) β-, γ-, *and* δ-*Hydroxyaldehydes and Ketones.* The best-known β-hydroxyaldehyde is aldol, a colourless syrup, which reduces Fehling's solution and ammoniacal silver nitrate and yields a phenylhydrazone. It is fairly easily dehydrated to yield the unsaturated aldehyde—crotonaldehyde. Homologous β-hydroxy-aldehydes behave similarly if there is a hydrogen combined with the α-carbon atom.

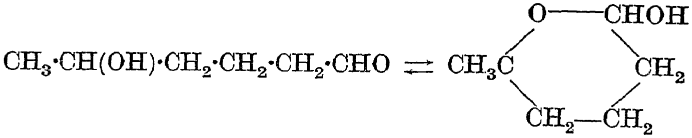
Recently it has been shown that δ- and γ-hydroxyaldehydes probably exist as an equilibrium mixture of a cyclic form and the normal open-chain form. Thus while they are able to reduce ammoniacal silver nitrate and are oxidised under suitable conditions to the corresponding acids, they restore colour to Schiff's reagent but slowly. Further, they yield hemiacetals instead of the expected normal acetals by treatment with methyl alcoholic hydrogen chloride. γ-Hydroxyvaleraldehyde is thus formulated



and its hemiacetal

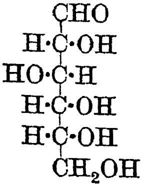


d-Hydroxycapraldehyde is similarly represented

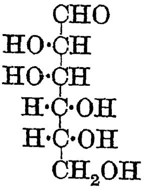


(Helferich, *Ber.*, 1919, **52**, 1123, 1800; Helferich and Lecher, *ibid.*, 1921, **54**, 930; Helferich and Gehrke, *ibid.*, p. 2640; Helferich and Malkomes, *ibid.*, 1922, **55**, 702; Helferich and Köster, *ibid.*, 1923, **56**, 2088; Helferich and Schäfer, *ibid.*, 1924, **57**, 1911).

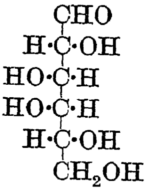
(c) *Reducing Sugars.*—Reducing sugars such as glucose (XI), mannose (XII), or galactose (XIII) were formerly represented as pentahydroxyaldehydes, in consequence of their reducing properties, their oxidation to the corresponding acids, their reduction to hexahydric alcohols, and their power to yield oximes, hydrazones, and cyanohydrins. These sugars differ from each other only in the spatial distribution of the –H and –OH groups :



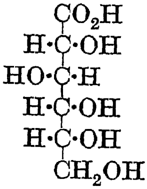
(XI.)



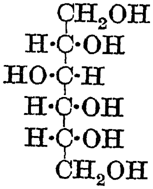
(XII.)



(XIII.)



(XIV.)



(XV.)

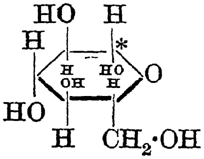
The analogy to the simple aldehydes, however, is not complete. Thus glucose and other reducing sugars have no action on Schiff's reagent: they do not furnish normal acetals by treatment with warm methyl alcoholic hydrogen chloride, but, instead, yield hemiacetals. From glucose, a mixture of two stereoisomeric hemiacetals or glucosides is formed, which are distinguished by the prefixes α- and β-. Both these compounds have no reducing properties, are stable to aqueous alkali, and are hydrolysed to glucose and methyl alcohol by dilute mineral acids. To account for these reactions, cyclic structures have been assigned to the α- and β-glucosides. It should be noted that the size of the ring structure can only be determined from a consideration of other evidence. Corresponding with the α- and β-glucosides there are two stereoisomeric forms of glucose also distinguished by the prefixes α- and β-. Many of the other reducing sugars are known in α- and β-forms and also have two series of glucosides derived from them. The following table summarises the physical constants of some of these.

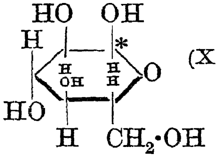
	Free sugar.		Methylglucosides.			
	α-Form.	β-Form.	α-Form.		β-Form.	
	$[\alpha]_D$.	$[\alpha]_D$.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	M. p.
Glucose . .	+111°	+ 17°	+158°	165—166°	—34°	110°
Mannose . .	+ 35	— 17	+ 82	193—194	—	—
Galactose .	+144	+ 52	+179	111—112	0	178—179
Xylose . .	+ 92	— 20 (calc.)	+153	90—92	—65	156
l-Arabinose .	+ 54 (calc.)	+174	—	176	—	116

The α- and β-forms of the reducing sugars exhibit mutarotation in aqueous solution, both forms reaching a value which represents the equilibrium between the two forms. The glucosides, on the other hand, do not exhibit mutarotation.

The experimental determination of the type of cyclic structure of the sugars is due to Haworth and his co-workers (Haworth, *Constitution of Sugars*, 1929). The normal forms of the reducing sugars have a six-membered ring, the hydrogens and hydroxyls being disposed above and below the mean plane of the ring. Combining this type of formula with the stereochemical structures worked out by E. Fischer, the following structures have been assigned to α-glucose (XVII) and β-glucose (XVI) :

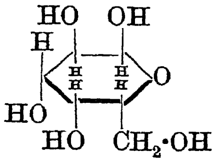
(XVI.)

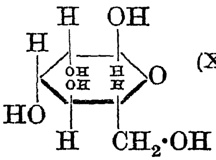




(XVII.)

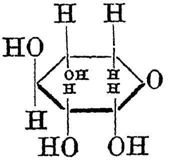
(XVIII.)

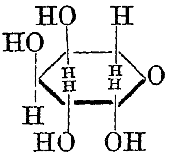




(XIX.)

(XX.)





(XXI.)

The difference between α- and β-forms of glucose is due to the relative dispositions of the hydrogen and hydroxyl about the carbon atom marked,* the reducing carbon atom. In the methyl glucosides, the hydroxyl group is converted into methoxyl, the α-glucosides being derived from α-glucose (E. F. Armstrong, *J.*, 1903, **83**, 1304). Similar conditions obtain in regard to the other reducing sugars, the formulæ of some of the more common being displayed above—galactose (XVIII), mannose (XIX), xylose (XX), arabinose (XXI). Evidently these sugars and their derivatives must also exist in α- and β-forms, although experimental proof of this is not complete for every reducing sugar.

Preparation of α- and β-Methylglucosides (α- and β-Methylglucopyranose).—A solution of anhydrous glucose (200 g.) in pure dry methyl alcohol (400 g.) containing approximately 12 g. of hydrogen chloride is boiled under reflux for 4½ hours. About 5 g. of decolorising charcoal are added shortly before the heating is complete, when the mixture is filtered rapidly and cooled by an external bath of ice. α-Methylglucoside separates as a thick paste of crystals, which are filtered under suction after ¾ hour. The filtrate is concentrated to about half its bulk and cooled in ice. A further amount of α-methylglucoside separates.

The filtrate (A) is reserved for the isolation of β-methylglucoside.

Both crops of crystals are combined and purified by crystallisation from methyl alcohol, m. p. 165—166°, [α] + 158°. The yield may amount to 90 g.

The filtrate (A) is cooled in a freezing mixture and nucleated with β-methylglucoside. The crude product which separates is collected and purified by crystallisation from methyl alcohol, m. p. 110°, [α] − 32°. The yield may be about 5 g.

The preparation of glucosides from acyl glucosyl halides is referred to later (pp. 179, 180).

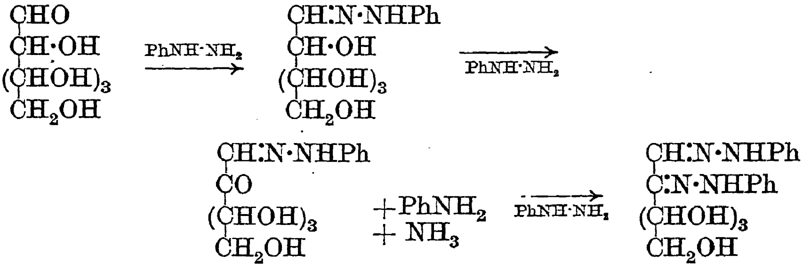
1. *Oxidation.*—By appropriate methods of oxidation, the aldoses are converted into monocarboxylic acids. This is generally accomplished by the action of chlorine or bromine on an aqueous solution of the sugar. Thus glucose furnishes gluconic acid, $CH_2(OH)\cdot(CH\cdot OH)_4\cdot CO_2H$ (Kiliani, *Annalen*, 1880, **205**, 182; *Ber.*, 1929, **62**, 589; Ling and Nanji, *J.S.C.I.*, 1922, **41**, 28T; E. Fischer, *Ber.*, 1890, **23**, 2625). Ketoses such as fructose appear to be more stable under these conditions.

Preparation of Gluconic Acid.—A solution of 10 g. of glucose in 50 c.c. of water is treated with 10 g. of bromine and the mixture kept for 1—2 days in a warm place. The mixture is then distilled under reduced pressure at 60° till the solution is colourless. The bromide content of the concentrated solution is determined and the free hydrobromic acid neutralised exactly by the addition of the necessary amount of sodium carbonate. The solution is then raised to boiling point and neutralised by the slow addition of calcium carbonate. The mixture is filtered and the filtrate kept in an ice-chest for 2 or 3 days. The calcium salt of gluconic, which has separated during this period, is obtained pure by crystallisation from water.

Under more vigorous conditions, oxidation occurs to yield dicarboxylic acids. Thus hexoaldoses give tetrahydroxyadipic acids, $CO_2H\cdot(CHOH)_4\cdot CO_2H$.

Preparation of Saccharic Acid.—Glucose (25 g.) is evaporated in a porcelain dish on a water-bath with 150 c.c. of dilute nitric acid (*d*, 1·15) till the residue is syrupy. It is dissolved in water, and the evaporation continued till the residue begins to become brown. It is then dissolved in 75 c.c. of water and neutralised with a concentrated solution of potassium carbonate. A 50% solution of acetic acid (12·5 c.c.) is then added and the solution concentrated to 40 c.c. After keeping at room temperature overnight, the acid potassium saccharate crystallises out. It is collected by filtration and crystallised from the least amount of hot water with the addition of decolorising charcoal.

2. *Action of Phenylhydrazine.*—In spite of the formulation of reducing sugars as cyclic compounds, they can react with phenylhydrazine to furnish phenylhydrazones, which by the further action of phenylhydrazine yield osazones. The formation of the osazone is preceded by the oxidation of the hydroxyl adjacent to the phenylhydrazino-group.



$$\begin{array}{l} \mathrm{CHO} \\ \mathrm{CH\cdot OH} \\ \mathrm{(CHOH)_3} \\ \mathrm{CH_2OH} \end{array} \xrightarrow{\mathrm{PhNH\cdot NH_2}} \begin{array}{l} \mathrm{CH{:}N\cdot NHPh} \\ \mathrm{CH\cdot OH} \\ \mathrm{(CHOH)_3} \\ \mathrm{CH_2OH} \end{array} \xrightarrow{\mathrm{PhNH\cdot NH_2}}$$

$$\begin{array}{l} \mathrm{CH{:}N\cdot NHPh} \\ \mathrm{CO} \\ \mathrm{(CHOH)_3} \\ \mathrm{CH_2OH} \end{array} \begin{array}{l} +\mathrm{PhNH_2} \\ +\mathrm{NH_3} \end{array} \xrightarrow{\mathrm{PhNH\cdot NH_2}} \begin{array}{l} \mathrm{CH{:}N\cdot NHPh} \\ \mathrm{C{:}N\cdot NHPh} \\ \mathrm{(CHOH)_3} \\ \mathrm{CH_2OH} \end{array}$$

The following conditions are of fairly general application for the preparation of osazones.

An approximately 10% aqueous solution of the reducing sugar (5 c.c.) is heated in a water-bath with phenylhydrazine (1 g.) dissolved in 1 c.c. of acetic acid diluted with 5 c.c. of water. Glucosazone, which results from mannose and fructose as well as glucose, separates from the hot reaction mixture. The osazones derived from lactose and maltose are more soluble and only separate after cooling the solution. For the reaction to go to completion, it is advisable to heat for about ½ hour in a boiling water-bath.

Although hydrazones and osazones are generally represented as derivatives of open-chain sugars, it is not improbable that they have a cyclic structure, for many of them have been observed to exhibit mutarotation in solution.

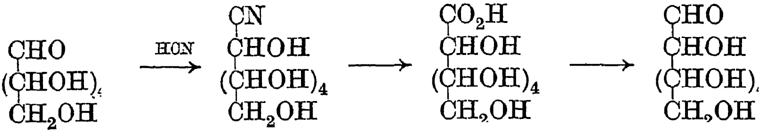
The crystalline habit of many osazones has frequently been used for the identification of the sugars which give rise to them. It should, however, be noted that the appearance of the crystals may be modified very considerably by the presence of impurities.

In general, the phenylhydrazones of reducing sugars are easily soluble in water. A notable exception is mannose phenylhydrazone, which is sparingly soluble and well suited to the separation and identification of mannose in mixtures.

Instead of phenylhydrazine, its *p*-bromo- and nitro-derivatives have been used as well as methylphenylhydrazine, diphenylhydrazine, and α-naphthylhydrazine for the characterisation and identification of reducing sugars.

Other manifestations of the reaction of reducing sugars as aldehydes are the formation of oximes and mercaptals (E. Fischer, *Ber.*, 1894, **27**, 673; Wohl, *ibid.*, 1891, **24**, 994).

Of particular interest is the reaction of the aldoses with hydrogen cyanide. A cyanohydrin is formed, comparable with those formed from simple aldehydes (Kiliani, *Ber.*, 1888, 21, 916). The importance of the reaction lies in the fact that by hydrolysis of the cyanohydrin and subsequent reduction of the lactone of the resulting acid an aldose is formed containing one carbon more than the original sugar (E. Fischer, *Ber.*, 1889, **22**, 2204).



$$\begin{array}{c}CHO\\(CHOH)_4\\CH_2OH\end{array} \xrightarrow{HCN} \begin{array}{c}CN\\CHOH\\(CHOH)_4\\CH_2OH\end{array} \longrightarrow \begin{array}{c}CO_2H\\CHOH\\(CHOH)_4\\CH_2OH\end{array} \longrightarrow \begin{array}{c}CHO\\CHOH\\(CHOH)_4\\CH_2OH\end{array}$$

3. *Reaction of the Sugars as Alcohols.*—Acetylation of the free hydroxyl groups of the sugars can be effected by treatment with acetic anhydride and pyridine or with acetic anhydride and sodium acetate. Less generally the acetylation is accomplished by the use of acetic anhydride and a catalyst such as zinc chloride or sulphuric acid. Other acyl groupings may be introduced in a similar manner.

The acylated reducing sugars are also ranged in α- and β-series corresponding with the free sugars.

The hydroxyl groups of the sugars can be converted into ether groupings by the action of methyl iodide and silver oxide (Purdie and Irvine, *J.*, 1903, **83**, 1021; 1904, **85**, 1049). In this reaction it is necessary to protect the reducing group from the oxidising action of the silver oxide by converting the sugar into its glucoside. By this process all the hydroxyls of the glucoside can be methylated with the formation, from a hexose, of a pentamethyl methyl glucoside. The same result is obtained if the methylation is effected by methyl sulphate in alkaline solution (Haworth, *J.*, 1915, **107**, 8). This reaction is of very considerable importance, inasmuch as it forms the basis of all the methods for establishing the points of linkage between the component sugars of the di- and tri-saccharides (Haworth, *Constitution of Sugars*, 1929).

An important reaction of the fully acetylated reducing sugars is the replacement of the acetoxy-group attached to the reducing carbon atom by chlorine or bromine by the action of halogen halide in acetic acid or in the liquid state (E. Fischer and E. F. Armstrong, *Ber.*, 1901, **34**, 2885).

Preparation of 2 : 3 : 4 : 6-Tetra-acetyl α-Glucosyl Bromide.—Acetic acid which has been saturated at 0° with dry hydrogen bromide (300 g.) is shaken with finely-powdered dry β-pentacetyl glucose (150 g.) till it has dissolved. The solution is then kept at room temperature for 2 hours, when it is diluted with 600 c.c. of chloroform and poured into 2 l. of ice-water, which is stirred mechanically. The chloroform layer is separated and the aqueous solution shaken with 150 c.c. of fresh chloroform. The combined chloroform solutions are washed with 1 l. of water, and then shaken with anhydrous calcium chloride till clear. The solution is then evaporated under reduced pressure and the residue treated with light petroleum (b. p. 40—60°). The glucosyl bromide separates out as long needles, which are collected by filtration. The product is purified by rapidly cooling a hot solution in the minimum amount of absolute alcohol. The crystalline paste which separates is filtered under suction and thoroughly washed with light petroleum to remove the last traces of alcohol. The substance must be kept in a vacuum desiccator over calcium chloride, m. p. 88°—yield about 120 g. (E. Fischer, *Ber.*, 1916, **49**, 584).

Other acylated sugars behave similarly, and the method has been used successfully for the preparation of the analogous derivatives from acetylated disaccharides. It should be noted that the α-series of halides are more stable than the β-series, and generally constitute the sole product, whether the α- or β-series of sugars are used as starting point. Indeed, the β-series of tetra-acetylglucosyl halides are but little known, owing to their instability and tendency to isomerise into the more stable α-series (E. Fischer and E. F. Armstrong, *Ber.*, 1901, **34**, 2885; Schlubach, *ibid.*, 1926, **59**, 840; Brigl, *ibid.*, p. 1588).

More stable members of the β-series of glucosyl halides are 2-trichloroacetyl-3 : 4 : 6-triacetyl β-glucosyl halide (Brigl, *Z. physiol. Chem.*, 1921, **116**, 1), and to a less degree 3 : 4 : 6-triacetyl-β-glucosyl chloride. The formation of glucosides even from these more stable compounds does not proceed uniformly, for the product may contain considerable proportions of the β-glucoside. Under special conditions the proportion of α-glucoside in the product may be raised to 90% (Brigl and Keppler, *Ber.*, 1926, **59**, 1588; Hickinbottom, *J.*, 1929, 1680; 1930, 1338).

The glucosyl halides are valuable synthetic agents in that the halogen may be replaced by a variety of other groupings. They are therefore extensively used for introducing acylated sugar residues into suitable molecules. It should be noted, however, that the stable α-series of halides generally yield β-glucosides.

Preparation of Tetra-acetyl-β-methylglucoside.—Tetra-acetyl α-glucosyl bromide is heated under reflux with an excess of dry methyl alcohol and about twice the theoretical amount of dried and finely-divided silver carbonate.

When the reaction is complete, the suspended silver bromide and unchanged silver carbonate are removed by filtration. Evaporation of the filtrate yields tetra-acetyl β-methylglucoside, m. p. 104—105°.

Preparation of Tetra-acetyl-β-benzylglucoside.—Tetra-acetyl α-glucosyl bromide (6 g.), 80 c.c. of dry ether, and 30 g. of benzyl alcohol, are mixed and shaken with the addition of 4 g. freshly-prepared dry silver oxide. When a test portion of the reaction solution no longer gives a precipitate of silver bromide when boiled with silver nitrate, the suspended matter is separated and the solvent distilled from the filtrate. The excess of benzyl alcohol is distilled off in steam. The residue of tetra-acetylbenzylglucoside solidifies on cooling. It is purified by crystallisation from aqueous alcohol, m. p. 96—101°, $[\alpha]_D$ − 49° (*c*, 2) (Fischer and Helferich, *Annalen*, 1911, **383**, 68).

Preparation of Tetra-acetyltheobromine-β-glucoside.—The silver derivative of theobromine (5 g.), which has been dried at 130°, is boiled for ½ hour with a solution of tetra-acetyl-α-glucosyl bromide (7·1 g.) in 100 c.c. of toluene. The precipitate of silver bromide is collected. Light petroleum (200 c.c.) is added to the filtrate. A pasty precipitate results. After standing, the supernatant solution is decanted off and the precipitate stirred with 50 c.c. of methyl alcohol.

The tetra-acetylglucoside separates as colourless needles, which are collected after cooling to 0°. It is purified by the addition of light petroleum to a solution in warm ethyl acetate, m. p. 180—240°, $[\alpha]_D$ − 18° (*c*, 6·8, tetrachloroethane) (Fischer and Helferich, *Ber.*, 1914, **47**, 210).

Preparation of ω-Hydroxy-4-β-tetra-acetylglucosyl Acetophenone.—A solution of the potassium salt of ω : 4-dihydroxyacetophenone (4 g.) in a mixture of water (40 c.c.) and acetone (40 c.c.) is treated, at room temperature, with a solution of tetra-acetyl-α-glucosyl bromide (8·5 g.) in 20 c.c. of acetone. The resulting clear solution is kept for 24 hours and the solvent then removed by evaporation under reduced pressure at temperatures below 30°. A viscous semi-solid residue results. After washing with water and then keeping in an ice-chest overnight, it is dissolved in a small amount of alcohol. The addition of water to produce a faint turbidity in the solution brings about the separation of the glucoside as flattened needles on keeping, m. p. 149—150° after further crystallisation (Léon, Robertson, Robinson, and Seshadri, *J.*, 1931, 2679).

The application of the acylated glucosyl halides to the synthesis of disaccharides is described in the following papers: Helferich and Klein, *Annalen*, 1926, **450**, 225; Helferich and Rauch, *Ber.*, 1926, **59**, 2656; *Annalen*, 1927, **455**, 168; Helferich and Schäfer, *ibid.*, 1926, **450**, 229; Helferich and Bredereck, *ibid.*, 1928, **466**, 166.

4. *γ-Sugars.*—The derivatives of the sugars which have already been discussed have a six-membered heterocyclic structure. Other derivatives are known having a five-membered heterocyclic structure. These are derived from the so-called γ-sugars. A more systematic and logical nomenclature, introduced by Haworth (compare Goodyear and Haworth, *J.*, 1927, 3140), distinguishes them by the term *furanose*. Thus γ-arabinose and γ-glucose are known as arabofuranose and glucofuranose, respectively. The evidence on which such structures are based is due almost entirely to the work of Haworth and his collaborators, and is summarised by Haworth (*Constitution of Sugars*).

The most accessible derivatives of this type are the methyl glucosides, which are prepared by the action of dry methyl alcoholic hydrogen chloride on the monosaccharide at room temperature (E. Fischer, *Ber.*, 1914, **47**, 1980; Haworth, Ruell, and Westgarth, *J.*, 1924, **125**, 2468; S. Baker and Haworth, *ibid.*, 1925, **127**, 365; Haworth and Westgarth, *ibid.*, 1926, 880). The glucosides thus obtained resemble those of the pyranose sugars in being indifferent to Fehling's solution and moderately concentrated alkali. One important difference is the extraordinary sensitiveness of the furanosides to dilute aqueous mineral acids. Thus ethyl glucofuranoside is completely hydrolysed by boiling for ½ hour with 0·01N-hydrochloric acid.

Preparation of Methylxylofuranoside (γ-Methyl Xyloside).—Finely sieved, dry xylose (11·9 g.) is dissolved in 238 g. of dry methyl alcohol containing approximately 1% of its weight of dry hydrogen chloride. The solution is kept at room temperature till it ceases to reduce Fehling's solution (5—7 days). The solution is then neutralised by adding an excess of dry finely-powdered silver carbonate, filtered, and evaporated under reduced pressure at a temperature not exceeding 40°. The residual syrup is then extracted several times with hot neutral ethyl acetate. Evaporation of the solvent from the extract at 40° under reduced pressure leaves a syrup of the crude glucoside, which is purified by distillation in high vacuum, b. p. 161°/0·03 mm., $[\alpha]_D + 63°$ in ethyl alcohol (Haworth and Westgarth, *loc. cit.*).

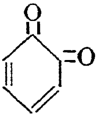
The product from this process consists of a mixture of α- and β-forms, probably contaminated with small amounts of the normal glucosides. Recently, Haworth and his co-workers have succeeded in isolating some of the γ-glucosides in a crystalline state. The following table compares the physical constants of some of the γ-glucosides.

	M. p.	$[\alpha]_D$ in water.
α-Methyl glucofuranoside	62—63°	+118°
α-Ethyl glucofuranoside	82—83	+101
β-Methyl glucofuranoside	liquid	− 77
β-Ethyl glucofuranoside	59—60	− 86
α-Methyl mannofuranoside	118—119°	+113

(Haworth and Porter, *J.*, 1929, 2796; 1930, 649; Haworth, Porter, and Waine, *ibid.*, 1932, 2254.)

(6) *Quinones.*

In the quinones there are two carbonyl groups, the carbon atoms of which are part of the aromatic nucleus and are situated either *ortho* or *para* to one another; *meta*-quinones are unknown. Formulæ I and II represent *o*- and *p*-benzoquinones, which can be considered to be diketo-derivatives of 1 : 2- and 1 : 4-dihydrobenzene, respectively. Polycyclic hydrocarbons also furnish quinones, and here the number of possible compounds is very great. Thus six naphthaquinones are theoretically possible, but so far only three are known, namely α- (formula III), β- (IV), and *amphi*-naphthaquinone (V). Attempts to prepare the other naphthaquinones have resulted in the formation of diquinones containing dinaphthyl residues (Morgan and Vining, *J.*, 1921, **119**, 1707; Stenhouse and Groves, *ibid.*, 1878, **33**, 418; compare Chattaway, *ibid.*, 1895, **67**, 657). Of the six theoretically possible anthraquinones, only three are known (formulæ VI, VII, VIII).



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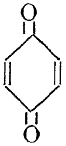

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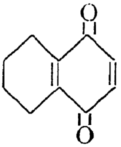

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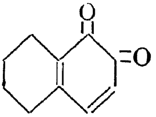

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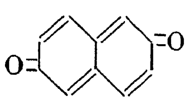

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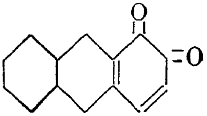

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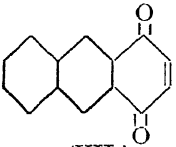

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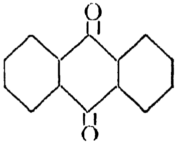
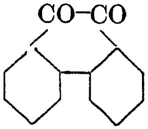


(VIII.)



(IX.)

Considerable differences in reactivity are shown by the different classes of quinones. *p*-Benzoquinone, in addition to yielding a large number of molecular compounds of the quinhydrone type, reacts with a variety of reagents such as hydrogen chloride and bromide, conjugated hydrocarbons, benzenesulphinic acid, alcohols, and primary amines. It is, moreover, very sensitive to aqueous alkalis and generally easily broken down by oxidising agents. The reactivity is no doubt due to presence of ethylenic bonds adjacent to the carbonyl, for the reactions of *p*-benzoquinone are shared by its homologues—except in so far as steric effects become evident.* α-Naphthaquinone behaves somewhat similarly. On the other hand, 9 : 10-anthraquinone (VIII), which has no true ethylenic linkages, is comparatively inert, and is indifferent to aqueous alkalis and to concentrated sulphuric acid at 100°; it is attacked but slowly by oxidising agents.

(a) *Reduction of Quinones.*—*o*- and *p*-Benzoquinones and similarly constituted quinones are reduced very readily to the corresponding dihydric phenols in aqueous solution by sulphur dioxide. Although naphthaquinones and phenanthraquinone are similarly reduced, α-naphthaquinone is not appreciably affected by cold aqueous sulphurous acid. It is best reduced by stannous chloride (Russig, *J. pr. Chem.*, 1900, [ii], **62**, 32). Anthraquinone is indifferent to aqueous solutions of sulphur dioxide.

The reduction of *p*-benzoquinone by sulphur dioxide is not quantitative. Only about 80% of the theoretically possible amount of quinol is obtained, the remainder of the product being quinolsulphonic acid, formed by the addition of sulphurous acid to quinone (Dodgson, *J.*, 1914, **105**, 2435).

Preparation of Quinol and of Quinolsulphonic acid from p-*Benzoquinone.*—A stream of sulphur dioxide is led into a solution of 5 g. of *p*-benzoquinone in 400 c.c. of water. When the reduction is complete, the solution is extracted several times with ether. Evaporation of the dried ethereal extracts yields quinol (4 g.).

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* Di*iso*amyl *p*-benzoquinone is stated to have no reaction with alkalis. It is also indifferent to phenylhydrazine, to hydrogen bromide in chloroform, and to aniline (Koenigs and Mai, *Ber.*, 1902, **25**, 2653).

The aqueous solution—after ether extraction—is boiled to remove dissolved ether and excess of sulphur dioxide, then neutralised with barium carbonate and filtered. The filtrate contains the barium salt of quinolsulphonic acid. It is treated with the necessary amount of sodium sulphate to precipitate all the barium and then filtered from the insoluble barium sulphate. Evaporation of the clear filtrate under reduced pressure yields the crude sodium salt of quinolsulphonic acid. It is purified by washing with ether, decolorising it with charcoal, and then crystallising from methyl alcohol. The salt separates from this solvent as almost white leaflets (yield about 1·5—1·7 g.) (Dodgson, *loc. cit.*).

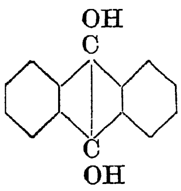
Benzoquinones may be also reduced by the action of an excess of phenylhydrazine or aqueous hydroxylamine, but these reagents are not so convenient as sulphurous acid. Reduction has also been effected by the use of zinc dust and acetic acid. 9 : 10-Anthraquinone, which is not changed by aqueous sulphur dioxide or phenylhydrazine, yields the corresponding dihydric phenol (X) by treatment with sodium hydrosulphite.

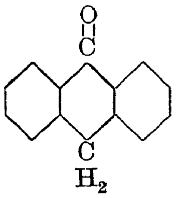
Reduction of 9 : 10-*Anthraquinone to* 9 : 10-*Anthrahydroquinone.*—A suspension of 2 g. of finely-divided anthraquinone in 10 times its weight of alcohol is boiled under reflux with a concentrated aqueous solution of 5 g. of sodium hydrosulphite. The colour of the anthraquinone rapidly changes to greenish yellow. The anthrahydroquinone is filtered off and washed. It is obtained as greenish-yellow needles, soluble in aqueous alkalis with the production of a deep red colour. This is easily oxidised to anthraquinone (Grandmougin, *Ber.*, 1906, **39**, 3563).

A red solution of a salt of anthrahydroquinone is obtained by reducing a suspension of anthraquinone in alkaline solution with hydrosulphite or zinc dust.

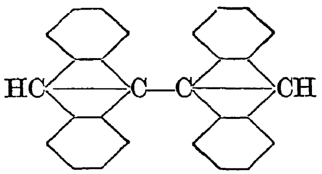
By the use of more vigorous conditions other products are formed from anthraquinone. Tin and hydrochloric acid in acetic acid solution yield anthranol (XI), together with some dianthryl (XII) (Liebermann and Gimbel, *Ber.*, 1887, **20**, 1854). A further product of the reduction of anthraquinone is dianthranol (XIII), which can be obtained by heating with zinc dust and alkali under pressure (H. Meyer, *Ber.*, 1908, **42**, 143; D.R.-P., 223,209).

(X.)

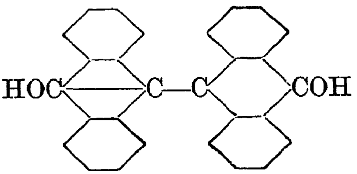




(XI.)

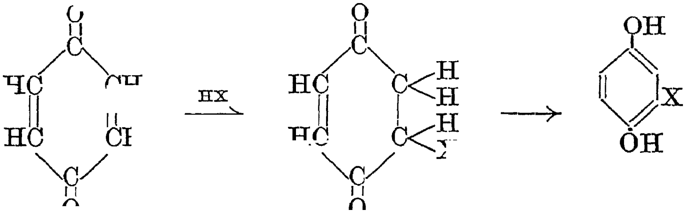


(XII.)



(XIII.)

(b) *Formation of Substituted Quinones and Quinols.*—*p*-Benzoquinone and similarly constituted quinones yield substituted quinols by reaction with substances of the general type R·H, where R = Br or Cl, $CH_3·CO_2$–, AlkO–, RNH–, Ph–, $Ph·SO_2$, etc. The general course of the reaction has been the subject of various interpretations (Bamberger and Blangey, *Annalen*, 1911, **384**, 287; Michael and Cobb, *J. pr. Chem.*, 1910, [ii], **82**, 298; Schmidlin, *Ber.*, 1911, **44**, 1700). Robinson (*Outline of an Electrochemical Theory of the Course of Organic Reactions*, 1932, p. 30) has recently suggested a mechanism based on considerations of electron changes. Apart from the ultimate mechanism of the reaction, the simplest method of representing these changes appears to be to consider them as preceded by the addition of the reagent to the double bond of the quinone. There is subsequently a rearrangement to a quinol:



It is possible to prepare compounds in which the double bonds are saturated by the addition of 2 or 4 atoms of bromine or chlorine (Sarauw, *Annalen*, 1881, **209**, 111; Nef, *J. pr. Chem.*, 1890, [ii] **42**, 182; T. H. Clark, *Amer. Chem. J.*, 1892, **14**, 553; Olivieri-Tortorici, *Gazzetta*, 1897, **27**, [ii], 572). *p*-Benzoquinone dibromide is slowly converted into 2 : 5-dibromoquinol in acetic acid solution (Sarauw, *loc. cit.*, p. 109).

Preparation of 2-Chloroquinol and 2 : 5-Dichloroquinol.—A stream of dry hydrogen chloride is passed into a not too concentrated solution of *p*-benzoquinone in dry chloroform till the brown precipitate which is first formed has been completely converted into white monochloroquinol. The product is collected by filtration and purified by crystallisation from chloroform, m. p 106°—yield 62 g. from 50 g. of quinone.

2-Chloroquinol, on oxidation with dichromate and dilute sulphuric acid yields chlorobenzoquinone, which by further treatment with dry hydrogen chloride furnishes 2 : 5-dichloroquinol (S. Levy and G. Schultz, *Annalen* 1881, **210**, 138; compare Wöhler, *ibid.*, 1844, **51**, 155).

Preparation of 2 : 5-Diethoxybenzoquinone.—*p*-Benzoquinone (5 g.) is heated under reflux with 24 g. of ethyl alcohol in which have been dissolved 6 g. of fused zinc chloride. The mixture becomes dark brown, and the reaction is complete when the alcohol refluxing from the condenser has become colourless A dark paste of crystals is obtained on cooling. The product is collected by filtration and crystallised from alcohol after treatment with decolorising charcoal. It separates as yellow platelets, m. p. 183°. 2 : 5-Dimethoxy- and 2 : 5-dipropoxy-quinones are prepared similarly (Knoevenagel and Bückel *Ber.*, 1901, **34**, 3994).

Preparation of Hydroxyquinoltriacetate.—Benzoquinone (60 g.) is added in small portions to a mixture of acetic anhydride (180 g.) and concentrated sulphuric acid (12 g.), which is stirred mechanically. The temperature of the mixture rises to 40—50°, and it is maintained between these limits by regulating the addition of the quinone. When all the quinone has been added, the solution is allowed to cool to about 25°, when it is poured into 750 c.c. of cold water. The precipitated triacetate is collected by filtration and crystallised from 250 c.c. of alcohol, m. p. 96—97°—yield 85—87% of theoretical (Thiele, *Ber.*, 1898, **31**, 1247; Vliet, *Organic Syntheses*, 1925, **4**, 36).

Preparation of 2 : 5-*Di*-m-*xylylquinol.*—Powdered anhydrous aluminium chloride (140 g.) is added to well-stirred *m*-xylene (375 g.) cooled to − 5° and thereafter 70 g. of dry powdered *p*-benzoquinone are added in portions of about 0·5 g. It is better to add the quinone fairly rapidly during the initial stages of the reaction—the temperature must be kept below 20°—for the solution eventually becomes very thick and can only be stirred with difficulty. The stirring is continued for 2 hours after all the quinone has been added, and the reaction mixture is kept in an ice-chest overnight.

It is then poured into a well-stirred mixture of 100 c.c. of hydrochloric acid and 400 c.c. of water. When the solid which separates under these conditions has become dark grey in colour and the excess of xylene has formed a separate layer, the product is collected by filtration and dried in a vacuum desiccator over phosphorus pentoxide. It is purified by heating with decolorising charcoal in benzene solution for 1 hour. After filtration, di-*m*-xylylquinol separates on cooling. A further crystallisation from benzene furnishes the product as white needle-like crystals, m. p. 188—189°—yield 30 g. (Browning and Adams, *J. Amer. Chem. Soc.*, 1930, **52**, 4102; compare Pummerer and Fiedler, *Ber.*, 1927, **60**, 1441).

Preparation of 2 : 5-*Di*-p-*tolylquinol.*—Aluminium chloride (67 g.) is added during 1 hour to a suspension of 21·6 g. of *p*-benzoquinone in 150 c.c. of toluene. The reaction mixture must be kept at 0° and stirred mechanically. It gradually changes in colour to brownish-black, and after 4 hours is poured into a mixture of crushed ice and hydrochloric acid. A light brown or greenish-grey precipitate is obtained consisting of crude 2 : 5-ditolylquinol. It is purified by solution in hot alcohol (200 c.c.), filtration through a hot funnel, and then boiling the filtrate with decolorising charcoal after adding some sulphur dioxide. After filtering, some water is added to precipitate the less soluble impurities. The quinol separates from the remainder of the solution as brownish crystals, which after several crystallisations from benzene are obtained as white crystals, m. p. 188°—yield 6·6 g. (Pummerer and Prell, *Ber.*, 1922, **55**, 3105).

Phenols and phenyl ethers may be used instead of hydrocarbons in this reaction (Pummerer and Prell, *loc. cit.*; Pummerer and Fiedler, *loc. cit.*).

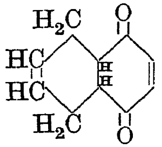
p-Benzoquinone combines readily with benzenesulphinic acid in aqueous solution to give 2 : 5-dihydroxydiphenylsulphone. Thymoquinone and β-naphthaquinone behave similarly, and it is claimed that benzenesulphinic acid can add itself, in general, to all *o*- and *p*-quinones whether substituted by alkyl or halogen, as long as they have a hydrogen in the nucleus capable of replacement (Hinsberg, *Ber.*, 1894, **27**, 3259; 1895, **28**, 1315).

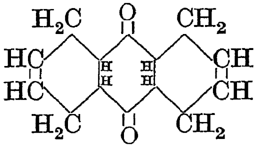
Amines, particularly aromatic amines, react with *p*-benzoquinone in a manner analogous to hydrogen chloride or benzenesulphinic acid to yield either 2-arylaminoquinols or 2 : 5-diarylaminoquinols, which are oxidised by the unchanged quinone in the reaction mixture to the corresponding quinones (A. W. Hofmann, *Proc. Roy. Soc.*, 1863, **13**, 4; Zincke, *Ber.*, 1883, **16**, 1556; Zincke and v. Hagen, *ibid.*, 1885, **18**, 785; H. and W. Suida, *Annalen*, 1918, **416**, 118).

Other reactions of an analogous type are the addition of alkali bisulphite to yield quinolsulphonic acids; thiosulphuric acid yields quinolthiolsulphuric acid (D.R.-P. 175,070); acetaldehyde and quinone exposed to sunlight furnish 2 : 5-dihydroxyacetophenone (Klinger and Kolvenbach, *Ber.*, 1898, **31**, 1214).

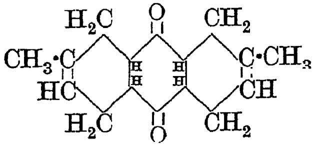
It has been known for some time that benzoquinone combined additively with *cyclo*pentadiene (Albrecht, *Annalen*, **1906**, **348**, 31). This reaction has recently been examined by Diels and his co-workers. They find that hydrocarbons with conjugated double bonds, such as butadiene, isoprene, *cyclo*pentadiene, and *cyclo*hexadiene react with *p*-quinones to fuse one or two rings to the double bonds of the quinone (compare p. 25). Thus butadiene and benzoquinone furnish (XIV) and (XV). Isoprene gives as the final product of the reaction a mixture of (XVI) and (XVII).

(XIV.)

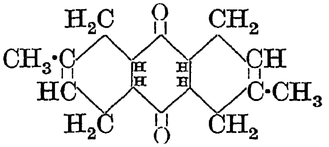




(XV.)



(XVI.)



(XVII.)

Products (XV), (XVI), and (XVII) can be oxidised to the corresponding aromatic quinone, (XV) yielding anthraquinone. This reaction is a most important one. It also occurs when the quinone is replaced by other substances containing the grouping $-\overset{|}{C}\vdots\overset{|}{C}\cdot CO$ (Diels and Alder, *Annalen*, 1928, **460**, 98; Diels, Alder, and Stein, *Ber.*, 1929, **62**, 2337; compare Diels and Alder, *Annalen*, 1931, **490**, 236 *et seq.*; *Ber.*, 1929, **62**, 554, 2081; *Annalen*, 1929, **470**, 62).

Preparation of 1 : 4-*Dihydro-α-naphthaquinone.*—An excess of butadiene is passed into a suspension of *p*-benzoquinone in dry benzene and the mixture kept for several days with occasional shaking. The quinone gradually dissolves, and the residue, after evaporating the solvent, is crystallised from light petroleum. The product (XIV) is obtained as a crystalline mass with a faint green colour, m. p. 58°.

It is isomerised to 1 : 4-dihydro-α-naphthahydroquinone by adding a trace of a solution of hydrogen bromide in acetic acid to the substance dissolved in an equal weight of acetic acid. There is a rise in temperature, and the solution sets to a paste of snow-white crystals. The hydroquinone separates from acetic acid in colourless needles, m. p. 212°.

It is oxidised to 1 : 4-dihydro-α-naphthaquinone by passing a vigorous current of air through a suspension in ferric chloride solution. The quinol rapidly goes into solution, and the quinone thus formed is isolated by steam distillation of the solution. After drying on porous earthenware it is recrystallised from light petroleum—yellow needles, m. p. 109°.

Preparation of Tetrahydroanthraquinone.—A solution of 12 g. of α-naphthaquinone in 15 c.c. of alcohol containing 4—5 g. of butadiene is heated in a sealed tube at 100° for 3 hours. The required product forms a crystalline mass in the tube. It is purified by crystallisation from alcohol or light petroleum, m. p. 105—106°.

Oxidation to anthraquinone is accomplished by warming with chromic acid in glacial acetic solution, or more conveniently by adding a few drops of alcoholic potash to an alcoholic solution of the tetrahydro-compound, and then passing a stream of air through the blood-red solution thus formed. Anthraquinone gradually separates.

(c) *Reactions of Quinones as Ketones.*—The normal action of free hydroxylamine on benzoquinones results in the formation of the corresponding quinol. The formation of oximes is generally accomplished by the action of hydroxylamine hydrochloride in aqueous alcoholic solution, mono- and di-oximes being obtained.

Preparation of p-*Xyloquinone-mono- and -di-oximes.*—A solution of 10 g. of *p*-xyloquinone in 300 c.c. of 80% alcohol is heated under reflux with 5 g. of hydroxylamine hydrochloride for 2 hours. After cooling and keeping for several hours a small quantity of the dioxime has separated. It is collected by filtration and the filtrate concentrated to about one-quarter its bulk. The monoxime separates on cooling, and is collected by filtration. A further quantity is obtained by addition of water to the filtrate. It crystallises from water as needles with a yellow tint, m. p. 163—165°.

The dioxime is obtained by heating the quinone with double the amount of hydroxylamine hydrochloride used for the preparation of the monoxime. The solution deposits the dioxime on cooling. It is purified by crystallisation from acetic acid. The m. p. recorded by different observers is between 254° and 273° (Goldschmidt and Schmid, *Ber.*, 1885, **18**, 568; Sutkowski, *ibid.*, 1887, **20**, 978).

Preparation of Thymoquinonedioxime.—A hot solution of nitrosothymol (thymoquinone monoxime) in alcohol is boiled under reflux with twice the theoretical amount of hydroxylamine hydrochloride. After about ¼ hour a dense pale-yellow crystalline precipitate commences to separate. When the separation appears to be complete, the mixture is cooled and the product collected by filtration. It is washed with cold alcohol, purified by solution in concentrated hydrochloric acid and precipitation with water. It is obtained after this treatment as white small crystals which decompose about 235° (Kehrmann and Messinger, *Ber.*, 1890, **23**, 3557).

Quinones appear to differ widely in the ease with which they yield oximes. From tetra-substituted quinones such as chlor- or brom-anil, dibromothymoquinone, and trichloroquinones, no oximes have been obtained, while from the 2 : 6-dichloro- or dibromo-*p*-benzoquinones only monoximes result (Kehrmann, *J. pr. Chem.*, 1889, [ii], **40**, 257; *Ber.*, 1888, **21**, 3315; 1890, **23**, 3557). In contrast to this, *p*-xyloquinone and 2 : 5-dichloro-*p*-benzoquinone furnish mono- and di-oximes.

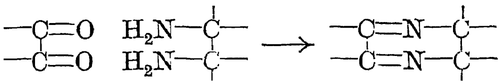
The quinones derived from polycyclic aromatic hydrocarbons can also react with hydroxylamine hydrochloride (H. Goldschmidt, *Ber.*, 1883, **16**, 2178). Anthraquinone is particularly resistant, withstanding the action of hydroxylamine hydrochloride in boiling alcoholic solution for a week. The monoxime results by heating at 180° in a sealed tube (Goldschmidt, *loc. cit.*, p. 2179). Mono- and di-oximes of acenaphthaquinone and phenanthraquinone have been prepared (Auwers and V. Meyer, *Ber.*, 1889, **22**, 1985; Francesconi and Pirazzoli, *Gazzetta*, 1903, **33**, [i], 36; compare Goldschmidt, *loc. cit.*; Rowe and J. S. H. Davies, *J.*, 1920, 1344).

p-Benzoquinone and its homologues are reduced to quinols by the action of phenylhydrazine or methylphenylhydrazine. α- and β-Naphthaquinones, however, react to give condensation products, that from the α-quinone and phenylhydrazine being identical with benzene azo-α-naphthol (Zincke and Bindewald, *Ber.*, 1884, **17**, 3026).

Nitrophenylhydrazines, in general, give rise to condensation products with the benzoquinones, but the products are identical with the isomeric hydroxy-azo-compounds. By using acyl derivatives of phenylhydrazine of the type $\genfrac{}{}{0pt}{}{\mathrm{Ph}}{\mathrm{Ac}}\!>\!\mathrm{N{\cdot}NH_2}$, the products obtained can only have the hydrazone structure. It is of interest, however, to note that such hydrazones suffer a rearrangement to the acyl derivatives of the hydroxy-azo-compounds by treatment of their ethereal solutions with solid potassium hydroxide (Willstätter and Veraguth, *Ber.*, 1907, **40**, 1432).

Benzoquinones react also with semicarbazide hydrochloride, but the products appear to have an azo-structure (Heilbron and J. A. R. Henderson, *J.*, 1913, **103**, 1404).

The formation of nuclear-substituted quinones by reaction with aniline and its homologues has already been referred to (p. 185). By using an excess of aniline in acetic acid solution or a mixture of aniline and aniline hydrochloride, *p*-benzoquinone is stated to yield anils of the aniloquinones (Zincke and v. Hagen, *Ber.*, 1883, **16**, 1558; 1885, **18**, 786). *ortho*-Quinones condense with diamines containing primary amino-groups on adjacent carbon atoms. Cyclic compounds containing the grouping (XVIII) are formed :



(XVIII.)

This reaction is of importance in that it provides a very convenient method of recognising *o*-diamino-compounds (see pp. 293–294).

Reaction of the benzoquinones with sodium bisulphite leads to the formation of quinolsulphonic acids. Phenanthraquinone and acenaphthaquinone, however, are soluble in bisulphite with the formation of bisulphite compounds, which are decomposed by acid with the regeneration of the original quinone.

Hydrogen cyanide does not appear to yield cyanohydrins with the benzoquinones, but furnishes cyanoquinols instead (Thiele and Meisenheimer, *Ber.*, 1901, **33**, 675). On the other hand, phenanthraquinone gives a dicyanohydrin (Japp and Miller, *Ber.*, 1883, **16**, 2417).

The Grignard reagent has been found to react with toluquinone and with *p*-xyloquinone to yield quinole derivatives, one of the carbonyls having been converted into $>\!\mathrm{C}\!<\genfrac{}{}{0pt}{}{\mathrm{CH_3}}{\mathrm{OH}}$ grouping. These substances are reactive and are converted partly into quinones and quinols by migration of the alkyl group (Bamberger and Blangey, *Annalen*, 1911, **384**, 272). Anthraquinone also reacts with the Grignard reagent, either one or both of the carbonyl groups being converted into $>\!\mathrm{C}\!<\genfrac{}{}{0pt}{}{\mathrm{Alk}}{\mathrm{OH}}$ or $>\!\mathrm{C}\!<\genfrac{}{}{0pt}{}{\mathrm{Ar}}{\mathrm{OH}}$ groupings (Guyot and Stähling, *Bull. Soc. chim.*, 1905, [iii], **33**, 1144; Haller and Guyot, *Compt. rend.*, 1904, **138**, 327, 1251).

(d) *Formation of Quinhydrones.*—The benzoquinones form well-defined molecular compounds with phenols. One of the first to be prepared was quinhydrone. It separates as a dark-green crystalline mass when cold aqueous solutions of quinol and *p*-benzoquinone are mixed. It is represented by the formula $O{:}C_6H_4{:}O,(HO{\cdot}C_6H_4OH)$. Many such compounds are now known in which benzoquinone or its homologues or halogen-substituted derivatives, or naphthaquinone, is combined with 1 molecule of a dihydric phenol or 2 molecules of a monohydric phenol. The place of the phenol may be taken by an aromatic hydrocarbon. Compounds of this type have more intense colours than their generators. A full account of the quinhydrones and references to the original papers can be found in *Organische Molekülverbindungen*, by P. Pfeiffer (1922, p. 199).

(e) *Estimation of Quinones.*—*p*-Benzoquinone and its homologues are in general solids with sharp or pungent odours and readily volatile in steam. The corresponding *ortho*-compounds, however, are not volatile. The same distinction applies to the α- and β-naphthaquinones. Both classes of quinones liberate iodine from acidified aqueous potassium iodide, and they can be estimated by use of this reaction. Apparently the liberation of iodine is not quantitative owing to an equilibrium being attained between the iodine, the quinone, hydrogen iodide, and the quinol formed by the reducing action of the hydrogen iodide. The procedure described below is claimed to give accurate results.

A 0·2—0·4% solution of the quinone in pure ether* is treated with 2 c.c. of a 30% aqueous solution of potassium iodide and 1 c.c. of 30% sulphuric acid for every 0·2 g. of quinone present. The estimation is carried out in a separating funnel with a perfectly ground stopper. The solution is now shaken for about 2 minutes, and when the two layers have separated, 50—60 c.c. of water are added. Immediately afterwards 0·1*N*-thiosulphate is added in portions of about 10 c.c. The solution is shaken after each addition of thiosulphate. As the colour of the mixture diminishes, the volume of succeeding portions of thiosulphate is reduced and it is stopped when the colour of the iodine has been discharged. A moderate excess of thiosulphate should be present (not more than 2 c.c.). The aqueous layer is now separated and the excess of thiosulphate titrated with iodine.

This method gives unsatisfactory results with quinones such as xyloquinone and thymoquinone which react but slowly with hydrogen iodide. By using a modification of this method, good results can, however, be obtained (Willstätter and Majima, *Ber.*, 1910, **43**, 1172).

Titanous chloride has been recommended for the estimation of quinones. The method consists in direct titration of a cold aqueous solution of the quinone with standardised titanous chloride using methylene blue as indicator. Instead of direct titration an excess of titanous chloride can be added and the excess ascertained by titration with ferric alum (Knecht and Hibbert, *New Reduction Methods in Volumetric Analysis*, 1918, p. 41).

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* The ether must be quite pure and free from peroxide.

TABLE X.—*Carbonyl Compounds.*

	B. p.	M. p.	*d.*	Phenyl-hydrazone. M. p.	*p*-Nitro-phenyl-hydrazone. M. p.	2 : 4-Dinitro-phenyl-hydrazone. M. p.	Semicarb-azone. M. p.	Oxime. M. p.	
Acetaldehyde	21°	—	—	—	128°	147°	162°	—	
Propaldehyde	49	—	$0{\cdot}817^{19}_{19}$	—	124	155	89	—	
Acrolein	52	—	$0{\cdot}841^{20}$	—	—	—	—	—	Polymerises on keeping.
Acetone	56	—	—	42°	148	128	187	59°	
*iso*Butaldehyde	63	—	$0{\cdot}792^{19}_{19}$	—	130	182	125	—	
n-Butaldehyde	75	—	$0{\cdot}805^{20}_{20}$	—	91	126	126	—	
Methyl ethyl ketone	78	—	—	—	128	115	135	—	
Diacetyl	88	—	$0{\cdot}980^{19}_{4}$	—	—	—	—	234*	Yellowish-green liquid, quinone-like odour; vapour has colour of chlorine; polymerises with ice-cold HCl.
2-Methylbutaldehyde	91	—	—	—	—	—	—	—	
*iso*Valeraldehyde	92	—	$0{\cdot}785^{20}_{20}$	—	101	123	—	—	
Methyl *iso*propyl ketone	94	—	—	—	—	—	—	—	
Diethyl ketone	101	—	—	—	139	156	139	—	
Methyl *n*-propyl ketone	102	—	—	—	—	141	—	—	
Crotonaldehyde	104	—	1·033	56	—	—	144	119	
n-Valeraldehyde	102	—	—	—	—	98	—	52	
Methyl *tert.*-butyl ketone	105	—	—	—	—	—	157	77	
Tiglic aldehyde	116	—	—	—	—	—	—	—	
Methyl *iso*butyl ketone	118	—	—	—	—	95	—	—	
Caproic aldehyde	128	—	—	—	—	104	—	51	
Methyl *n*-butyl ketone	128	—	—	—	—	106	—	—	
Mesityl oxide	130	—	$0{\cdot}858^{20}_{4}$	—	133	—	156	—	
Acetyl acetone	139	—	—	—	—	—	—	149*	$NH_2OH,HCl \longrightarrow$ dimethyl*iso*oxazole, b. p. 141°, and dioxime; $PhNHNH_2 \longrightarrow$ 3 : 5-dimethylphenylpyrazole, b. p. 273°; $FeCl_3 \longrightarrow$ intense red.
Oenanthaldehyde	154	—	0·832	—	—	106	109	58	
*cyclo*Hexanone	155	—	0·947	77 dec.	146	—	166	88	
Furfural	161	—	—	97	127	202	202	—	
2-Methyl*cyclo*hexanone	163	—	0·925	—	—	—	—	—	
Diacetone alcohol	164	—	—	—	—	—	—	56	Distils with trace of I $\longrightarrow$ mesityl oxide.
3-Methyl*cyclo*hexanone	168	—	0·911	—	—	—	180	oil	
4-Methyl*cyclo*hexanone	169	—	0·933	—	—	—	197	39	
Methyl hexyl ketone	171	—	—	—	—	58	—	—	
n-Octaldehyde	172	—	$0{\cdot}826^{20}_{20}$	—	—	—	98	—	
Benzaldehyde	179	—	—	158	192	235	214	35	Azine, m. p. 93°; hydrobenzamide, m. p. 110°.
Pelargonic aldehyde	81/ 13 mm.	—	$0{\cdot}827^{19}_{19}$	—	—	96	—	63	
Methyl heptyl ketone	191	—	—	—	—	—	—	—	
Fenchone	193	—	0·947	—	—	—	183	165	
Acetonyl acetone	194	—	$0{\cdot}983^{17}_{4}$	—	—	—	—	134*	
Salicylaldehyde	196	—	—	142	233	248	231	57	
m-Tolylaldehyde	199	—	$1{\cdot}024^{22}$	—	—	—	216	—	
Phorone	197	28°	—	—	—	—	186	—	Br in $CCl_4 \longrightarrow$ tetrabromide, m. p. 88°.
o-Tolylaldehyde	200	—	—	—	—	—	224	49	
Aldol	77/ 16 mm.	—	—	—	—	—	194	—	
a-Thujone	200	—	—	—	—	—	186	—	
β-Thujone	—	—	—	—	—	—	171	55	
p-Tolylaldehyde	204	—	$1{\cdot}072^{12}$	—	—	—	234	—	Azine, m. p. 155°; hydro-*p*-tolylamide, m. p. 95°.
Acetophenone	202	20	$1{\cdot}027^{25}_{25}$	105	184	—	167	59	
Camphor	204	175	—	233 dec.	—	—	237	118	
Decylaldehyde	93/ 12 mm.	—	—	—	—	—	—	69	Azine, m. p. 34°.
Menthone	206	—	—	—	—	—	184	59	
Citronellal	206	—	$0{\cdot}855^{20}$	—	—	—	83	oil	
Propiophenone	210	—	—	—	—	—	—	—	
Phenylacetaldehyde	193	—	$1{\cdot}025^{20}$	—	—	—	156	103	
Piperitone	117/ 20 mm.	—	$0{\cdot}934^{20}_{4}$	—	—	—	—	—	
Geranial	119/ 20 mm.	—	$0{\cdot}890^{20}$	—	—	—	164	—	Geranial-*β*-naphthocinchonic acid, m. p. 199°.
Neral	117/ 20 mm.	—	$0{\cdot}889^{20}$	—	—	—	171	—	
Cinnamaldehyde	221	—	—	168	195	—	215	138	
Pulegone	221	—	0·936	—	—	—	—	—	Bisnitrosopulegone, m. p. 81° (Baeyer and Henrich, *Ber.*, 1895, 28, 653).
n-Butyrophenone	222	—	—	—	—	—	—	—	
a-Ionone	124/ 11 mm.	—	$0{\cdot}932^{20}$	—	—	—	137	90	Odour of violets; *p*-bromophenylhydrazone, m. p. 142°.
β-Ionone	140/ 18 mm.	—	$0{\cdot}946^{17}$	—	—	—	149	—	Odour of violets; *p*-bromophenylhydrazone, m. p. 117°.
Carvone	230	—	$0{\cdot}961^{18{\cdot}7}_{4}$	—	—	—	163	72	$[a]^{D}$ ±62°; characteristic odour.
Cuminaldehyde	235	—	—	—	—	—	—	—	
Anisaldehyde	248	—	—	—	—	—	—	—	
m-Chlorobenzaldehyde	213	17	—	—	—	—	—	70	
p-Chloroacetophenone	230	20	—	—	—	—	—	—	
Piperonal	263	37	—	100	—	—	230	110	
Benzal acetone	262	41	—	156	166	—	—	115	
o-Nitrobenzaldehyde	—	44	—	—	—	—	—	103	
Thymoquinone	—	45	—	—	—	—	—	—	Hydroquinone, m. p. 139°.
Benzophenone	—	48	—	137	154	229	164	—	
Chloral hydrate	—	57	—	—	—	—	—	—	
m-Nitrobenzaldehyde	—	58	—	—	—	—	—	118	Azine, m. p. 125°.
Benzoyl acetone	—	61	—	—	—	—	—	—	$NH_2OH \longrightarrow$ 3-methyl-5-phenyl*iso*oxazole, m. p. 43°; hydrolysis with $NaOH \longrightarrow PhCOMe$; $FeCl_3 \longrightarrow$ intense red.
Toluquinone	—	68	—	—	—	—	—	—	Hydroquinone, m. p. 124°.
Vanillin	285	80	—	105	—	—	229	117	
Benzil	347	95	—	225*	290*	—	—	237*	
m-Hydroxybenzaldehyde	—	104	—	—	—	—	—	—	
p-Nitrobenzaldehyde	—	106	—	—	—	—	—	—	Azine, m. p. 300° *circa*.
p-Benzoquinone	—	115	—	—	—	—	—	—	
p-Hydroxybenzaldehyde	—	115	—	177	—	157	224	72	
Benzoin	343	130	—	106	—	—	—	151	Benzoyl derivative, m. p. 125°.
Trichloro-*p*-benzoquinone	—	165	—	—	—	—	—	—	
Camphorquinone	—	198	—	—	—	—	—	—	
Phenanthraquinone	—	202	—	—	—	—	—	—	Oxidation $\longrightarrow$ diphenic acid, m. p. 229°.
Anthraquinone	—	273	—	—	—	—	—	—	
Tetrachloro-*p*-benzoquinone	—	290†	—	—	—	—	—	—	

* Denotes di-derivative. † In sealed tube.

TABLE XI.

Carbohydrates.

	Free sugar, $[\alpha]_D$ in water.			Fully acetylated sugar.		Methylglucoside.				Fully acetylated methylglucoside.				
						α-Form.		β-Form.		α-Form.		β-Form.		
	α-Form.	β-Form.	Equilibrium mixture.	α, m. p.	β, m. p.	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	
l-Arabinose	—	+174°	+105°	—	—	174°	+245°	116°	+ 73°	—	—	—	—	Phenylosazone, m. p. 166°; acetobromoarabinose, m. p. 137°.
l-Xylose	+ 92°	—	+ 19	59°	126°	91	+153	156	− 66	—	—	115°	− 60° $CHCl_3$.	Phenylosazone, m. p. 163°; acetobromoxylose, m. p. 102°.
Rhamnose	− 8	—	+ 8	—	—	108	− 62	140	+ 95	—	—	—	—	Phenylosazone, m. p. 185°; acetobromorhamnose, m. p. 71°.
Glucose	+111	+ 17	+ 52	112	134	166	+159	110	− 34	100°	+137°	104	− 27 Alcohol.	Acetobromoglucose, m. p. 88°; phenylglucosazone, m. p. 210°.
Mannose	+ 35	− 17	+ 14	64	115	194	+ 82	—	—	—	—	—	—	
Fructose	—	−130	− 92	—	—	—	—	120	−172	—	—	76	−124 $CHCl_3$.	
Galactose	+144	+ 52	+ 80	—	142	111	+179	173	0	—	—	93	− 19	Phenylosazone, m. p. 186°; acetobromogalactose, m. p. 82°.
Maltose (anhydr.)	—	+118	+136	125	158	—	—	110	+ 79	—	—	186	− 26	Phenylosazone, m. p. 206°; acetobromomaltose, m. p. 84°.
Gentiobiose	+ 31	− 11	+ 10	188	192	—	—	98	− 36	—	—	65	—	Phenylosazone, m. p. 162°; acetobromogentiobiose, m. p. 131°.
Cellobiose	—	+ 16	+ 35	228	202	—	—	193	− 19	—	—	—	—	Phenylosazone, m. p. 198°; acetobromocellobiose, m. p. 180°.
Lactose	+ 90	+ 35	+ 55	152	90	—	—	170	—	—	—	—	—	Phenylosazone, m. p. 200°; acetobromolactose, m. p. 105°.
Melibiose	—	+124	+143	177	—	—	—	—	—	—	—	—	—	Phenylosazone, m. p. 178°.
Trehalose (anhydr.)	+197	no mutarotation		97		—	—							
Sucrose	+ 66			67		—	—							
Raffinose (anhydr.)	+123			100		—	—							

CHAPTER V

CARBOXYLIC ACIDS

- (1) General Reactions.
  - (*a*) Formation of Salts.
  - (*b*) Formation of Acyl Halides.
  - (*c*) Formation of Acid Anhydrides.
  - (*d*) Formation of Amides.
  - (*e*) Formation of Esters.
  - (*f*) Preparation of Aldehydes and Ketones from Acids.
  - (*g*) Behaviour of Acids and their Salts on Electrolysis.
  - (*h*) Elimination of the Carboxyl Group.
- (2) Special Reactions of the Commoner Groups of Carboxylic Acids.
  - (*a*) Fatty Acids.
  - (*b*) Aromatic Acids.
  - (*c*) Unsaturated Acids.
  - (*d*) Hydroxy Acids.
    - 1. α-Hydroxy-Acids.
    - 2. β-Hydroxy-Acids.
    - 3. γ-Hydroxy-Acids.
    - 4. Phenolic Acids.
  - (*e*) Keto Acids.
    - 1. α-Keto-Acids.
    - 2. β-Keto-Acids.
    - 3. γ-Keto-Acids.

CARBOXYLIC acids have the characteristic group $-CO \cdot OH$, the hydrogen of which can ionise in aqueous solution and is replaceable by metals. Those carboxylic acids which are appreciably soluble in water are therefore recognisable by their acidic reaction to neutral litmus and by the liberation of carbon dioxide from solutions of metal carbonates and bicarbonates. Acids insoluble in water show the same reactions in aqueous alcohol. The carboxyl group has therefore well-marked acidic properties. The strength of any particular acid is determined by the type and nature of the grouping attached to the carboxyl group. The following table illustrates this :—

	$k \,.\, 10^4$.		$k \,.\, 10^4$.
Formic	2·1	Crotonic	0·20
Acetic	0·18	Oxalic	380
Propionic	0·15	Malonic	17·7
Butyric	0·16	Succinic	0·74
Chloroacetic . .	15·5	Glutaric	0·46
Bromoacetic . .	13·8	Benzoic	0·6
Dichloroacetic . .	514	*o*-Nitrobenzoic . .	61·6
Trichloroacetic . .	1500	*m*-Nitrobenzoic . .	3·5
α-Chlorobutyric . .	14	*p*-Nitrobenzoic . .	4·0
β-Chlorobutyric . .	0·89	*o*-Hydroxybenzoic .	10·2
γ-Chlorobutyric . .	0·26	*m*-Hydroxybenzoic .	0·87
Glycollic	15·2	*p*-Hydroxybenzoic .	0·29
Lactic	13·8	*o*-Chlorobenzoic . .	13·2

The values for the dibasic acids are the first ionisation constant k_1.

The most important further reactions of the carboxyl group are replacement of the –OH by halogen, and by amino-groups and its conversion into –OAlk and –OAr. It should be noted that although there is a carbonyl group present, its typical reactions are almost entirely suppressed by the adjacent hydroxyl group.

1. *General Reactions.*

(a) *Formation of Salts.*

In general, salt formation is achieved by neutralisation of the acid with the appropriate hydroxide or carbonate. For the preparation of the salts of the alkali metals both methods are applicable, although it is generally more accurate to neutralise the acid with the alkali hydroxide using phenolphthalein as indicator. Salts of the alkaline earths and heavy metals which are soluble in water are prepared by treatment of the acid with an excess of an aqueous suspension of the appropriate carbonate, followed by filtration after boiling, and subsequent evaporation to crystallising point. To obtain sparingly soluble salts the general method is by double decomposition between a soluble salt of the acid and a suitable inorganic salt.

The preparation of silver salts of organic acids is frequently carried out. These salts are generally sparingly soluble and, with suitable precautions, are easily obtained pure. The usual method of preparation consists in adding an aqueous solution of silver nitrate to an aqueous solution of the ammonium salt of the acid. From a knowledge of the silver content of the pure dry salt—determined by cautious ignition—the molecular weight of the acid can be calculated if the basicity of the acid is known.

The analysis of other salts furnishes the same results, but it is obvious that the salts must be pure and not liable to form basic salts. Titration of the acid against standard alkali using phenolphthalein can also be used for this purpose, but here also it is necessary to know the basicity of the acid.

(b) *Formation of Acyl Halides.*

Replacement of the carboxylic hydroxyl to yield an acid chloride of the general formula $R{\cdot}CO{\cdot}Cl$ is effected by reaction with phosphorus halides or with thionyl chloride. If phosphorus pentachloride is used, approximately equimolecular proportions of the chloride and the acid or its salt are mixed. After the initial reaction has subsided, the formation of the acid chloride may be completed by warming :

$$R{\cdot}CO{\cdot}OH + PCl_5 \longrightarrow R{\cdot}CO{\cdot}Cl + HCl + POCl_3$$

Phosphorus oxychloride is eliminated from the product by fractionation.

If the acyl chloride is not appreciably volatile at 120°, the phosphorus oxychloride can be removed by heating the product to this temperature in a stream of nitrogen, or, alternatively, by evaporation under reduced pressure at 80—100°. Obviously phosphorus pentachloride cannot be conveniently used for the preparation of acyl chlorides the boiling points of which approximate to that of phosphorus oxychloride. In such circumstances phosphorus trichloride may be employed.

Phosphorus halides have the disadvantage that the product is liable to be contaminated with unchanged phosphorus trichloride or phosphorus oxychloride. A more convenient reagent is thionyl chloride, which is converted into gaseous products by reaction with acids. The following examples illustrate the general use of these reagents.

Preparation of n-*Butyryl Chloride.*—Phosphorus trichloride (53 g.) is added gradually from a tap funnel to butyric acid (100 g.), which is contained in a round-bottomed flask fitted with a condenser. The mixture is heated under reflux for about 1 hour, and then cooled. The butyryl chloride is decanted from the lower syrupy layer of phosphorous acid and then carefully fractionated. Alternatively the chloride may be distilled directly from the reaction mixture. If this is done, the treatment with the trichloride is best carried out in a distillation flask.

Preparation of Benzoyl Chloride (1).—Finely-powdered dry benzoic acid (100 g.) is mixed with 180 g. of powdered phosphorus pentachloride. When the initial reaction has subsided it is completed by heating on a steam-bath for about an hour. The phosphorus oxychloride is then removed by evaporation under reduced pressure at about 80°. The residue yields benzoyl chloride, b. p. 196—198°, by distillation at atmospheric pressure.

Preparation of Benzoyl Chloride (2).—Benzoic acid (20 g.) is heated at 100° with thionyl chloride (30 c.c.) in a 100-c.c. distillation flask fitted with a reflux condenser in the neck and canted so that the side arm of the flask is horizontal. The side arm is plugged by a cork.

When the evolution of hydrogen chloride and sulphur dioxide ceases, the reaction mixture is distilled, benzoyl chloride being collected at 192—198°.

Preparation of Oxalyl Chloride.—90 G. of finely-powdered anhydrous oxalic acid are intimately mixed with 400 g. of phosphorus pentachloride. The mixture must be cooled by an external bath of ice. Afterwards it is kept at room temperature till the whole mass is liquid, when it is fractionally distilled. Crude oxalyl chloride is collected between 60° and 100°. Several fractionations yield pure oxalyl chloride, b. p. 63—64°—yield 45—50% of the theoretical (Staudinger, *Ber.*, 1908, **41**, 3563).

Preparation of n-*Butyryl Chloride.*—A 150-c.c. distillation flask which has a long side arm fitted with a water-jacket is inclined so that the side arm acts as a reflux condenser. A dropping funnel is fixed in the neck of the flask by a rubber bung. Thionyl chloride is placed in the flask (56 g.), which is heated on a water-bath. *n*-Butyric acid (35 g.) is slowly added from the funnel during 1 hour. After all the acid has been added the heating is continued for ½ hour before distilling from an oil-bath. The distillate gives pure *n*-butyryl chloride after a further distillation, b. p. 100—101°. The yield is approximately equal to the weight of the acid used (Helferich and Schaefer, *Organic Syntheses*, 1929, **9**, 32).

(c) *Formation of Acid Anhydrides.*

The classical method for the preparation of acid anhydrides, introduced by Gerhardt (*Annalen*, 1853, **87**, 65, 149), consists in heating the acid chloride with a salt of the same acid :

$$R\cdot CO\cdot Cl + NaO\cdot CO\cdot R \longrightarrow (R\cdot CO)_2O + NaCl$$

A modification of this process, which is used technically, is to treat a salt of the acid with sufficient phosphorus oxychloride, phosphorus trichloride, thionyl chloride, or sulphuryl chloride to convert half of the salt into acid chloride (compare Gerhardt, *loc. cit.*; Denham and Woodhouse, *J.*, 1913, **103**, 1861). The reaction then follows the course indicated above. Another modification is to treat the acid chloride with pyridine (Wedekind, *Ber.*, 1901, **34**, 2070).

The anhydrides of the fatty acids, aromatic acids, and dibasic acids may be conveniently prepared by heating with acetyl chloride or acetic anhydride (Anschütz, *Annalen*, 1884, **226**, 1; Autenrieth, *Ber.*, 1901, **34**, 176; Kaufmann and Luterbach, *ibid.*, 1909, **42**, 3483; Fournier, *Bull. Soc. chim.*, 1909, [iv], **5**, 922).

Preparation of the Anhydrides of the Fatty Acids using Acetyl Chloride.—This method has been applied successfully to the preparation of anhydrides of many of the acids from propionic to *iso*amylacetic (Fournier, *loc. cit.*).

The fatty acid is placed in a flask fitted with a tap funnel and a fractionating column. It is heated to 120° by an oil-bath. Acetyl chloride is added from the tap funnel and the temperature of the oil-bath raised progressively to 180°, the whole operation taking about 10 hours. The product is then fractionated under reduced pressure. The yields vary between 55 and 75% of the theory.

The general method of using acetic anhydride consists in heating the acid with two or three times its weight of acetic anhydride under reflux for 4—6 hours and then fractionating the product.

Preparation of Benzoic Anhydride.—A mixture of 150 g. of benzoic acid and 150 g. of acetic anhydride is slowly distilled through a fractionating column so that the thermometer at the head of the column does not record a temperature greater than 120°. When about 25 c.c. of distillate have been collected, an equal volume of acetic anhydride is added to the reaction mixture from a tap funnel. The distillation is continued and a further quantity of 25 c.c. of acetic anhydride added after a further amount of 25 c.c. of distillate has been obtained.

The fractionation is now continued with the object of freeing the product from acetic acid and acetic anhydride. Distillation of the residue under reduced pressure furnishes crude benzoic anhydride, b. p. 210—220°/20 mm., and an intermediate fraction. From this latter, further amounts of benzoic anhydride can be obtained by systematic fractionation.

The crude benzoic anhydride is purified by crystallisation from benzene containing light petroleum. The yield of pure anhydride may amount to 100 g., m. p. 43° (Clarke and Rahrs, *Organic Syntheses*, 1923, **3**, 21; compare Kaufmann and Luterbach, *loc. cit.*).

The anhydrides of succinic and phthalic acids and their alkyl-substituted derivatives result by simple distillation with acetic anhydride. Although succinic and glutaric acids yield normal anhydrides by this method, the products from the higher homologues such as adipic, pimelic, suberic, azelaic, and suberic acids are polymerised (Hollemann and Voermann, *Proc. K. Akad. Wetensch. Amsterdam*, 1903, **6**, 410; Voermann, *Rec. trav. chim.*, 1904, **23**, 265; Blaise and Houillon, *Bull. Soc. chim.*, 1906, [iii], **35**, 199).

(d) *Formation of Amides.*

The general methods for the preparation of amides include the reaction of acyl halides, anhydrides or esters, with amines or ammonia; the elimination of the elements of water from an amine salt by heating or by distillation. It is also possible to replace the amino-group of some amides by other amino-groups. These processes are of the same general type and are represented by the scheme:

$$R{\cdot}CO{\cdot}X + NHR'R'' \qquad R{\cdot}CO{\cdot}NR'R'' + HX$$

(where $X = OH$, halogen, OAlk, NH_2. R' and $R'' = H$, alkyl or aryl).

One of the oldest of these methods consists in heating or distilling the ammonium salt of a suitable acid (Dumas, *Ann. Chim.*, 1830, [ii], **44**, 130). Thus, acetamide is obtained by submitting ammonium acetate to prolonged heating either in a sealed tube at 250°, or under reflux, followed by distillation. Amides and alkyl amides of homologues of acetic acid may be similarly prepared (A. W. Hofmann, *Ber.*, 1882, **15**, 977). The disadvantage of this method is that an equilibrium is attained between the salt, the amide, and the water, with the result that the yields are often seriously short of the theoretical. A more efficient and economical method consists in continuously removing the water as it is formed. The process is illustrated by the following.

Preparation of Acetamide.—A mixture of commercial ammonium acetate (100 g.) and glacial acetic acid (75 g.) is gently heated in a round-bottomed flask fitted with a rod and disk column, to which is attached a condenser. The heating is regulated so that the mixture is maintained just short of its boiling point for about 1 hour. Then the temperature is raised so that a very slow distillation takes place, the thermometer at the head of the column being kept at 103—104°. When 100 c.c. of distillate have been collected, the distillation is stopped and the residue in the flask transferred to a distillation flask and distilled. Approximately pure acetamide passes over between 195° and 225°. This fraction solidifies on cooling. It is drained on a Buchner funnel and dried on porous earthenware. The filtrate furnishes a further amount of acetamide on refractionating (François, *J. Pharm. Chim.*, 1906, [vi], **23**, 230; W. A. Noyes and Goebel, *J. Amer. Chem. Soc.*, 1922, **44**, 2294).

The acyl derivatives of the primary arylamines can be prepared from the amine and the fatty acid by a similar process, except that the product is usually isolated by pouring into water. The sparingly soluble derivative is then obtained as a crystalline solid. This method is frequently used for the characterisation of the fatty acids, but for this purpose a moderate excess of the amine is used instead of an excess of acid.

Preparation of n-*Butyro*-p-*toluidide.*—*n*-Butyric acid (1 g.) is heated with twice its weight of *p*-toluidine under reflux for about 1 hour. The product is poured into water acidified with hydrochloric acid and the precipitate collected. After washing with water it is purified by crystallisation from aqueous alcohol, m. p. 73—74°.

This method may also be used for the preparation of the anilides of the higher fatty acids and aromatic acids. When the acids are sparingly soluble in water, the product must be washed not only with dilute acid to remove excess of arylamine, but subsequently with dilute sodium carbonate solution to free it from unchanged organic acid.

The preparation of simple amides of the type $R{\cdot}CO{\cdot}NH_2$ by reaction of acyl chlorides with ammonia is of wide application. In its simplest form it consists in adding the acyl chloride to concentrated aqueous ammonia. This is often employed for the characterisation of the monobasic acids. For this purpose, the acid chloride need not be isolated. The following general directions are given by Aschan (*Ber.*, 1898, 31, 2344). They have been tried for normal fatty acids from acetic to stearic, and also for one or two unsaturated acids and for dibasic acids such as sebacic and suberic.

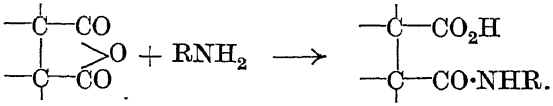
The acid is warmed with phosphorous trichloride till reaction ceases. After cooling, the crude acyl chloride is decanted from the syrupy layer of phosphorous acid and added drop by drop to concentrated aqueous ammonia contained in a flask and cooled in a mixture of ice and salt. It is recommended that the addition of the acyl chloride should be regulated so that none of the mist of ammonium chloride escapes from the flask. The mixture is then kept overnight. With a few exceptions, the amide separates in a crystalline state. With the amides of acetic, propionic, and butyric acids, which are soluble in water, the product is evaporated to dryness and the amide extracted from the residue by treatment with absolute alcohol.

For the preparation of anilides, in order to characterise monobasic acids, the following process has advantages over the usual method of heating the acid with the arylamine under reflux.

The acid is heated under reflux with about its own weight of thionyl chloride. After 1 hour, the product is cooled, diluted with ether, and an excess of aniline or *p*-toluidine in ethereal solution is added. The solution is cooled during this operation. A precipitate of the amine hydrochloride together with derivatives of sulphurous acid result. These are removed by shaking the suspension first with water and then with dilute hydrochloric acid (6% concentration). Evaporation of the ethereal solution yields the anilide.

The general application of acyl chlorides and anhydrides to the preparation of amides is considered more fully on pp. 262–265.

The anhydrides of dibasic acids with the carboxyl groups attached to adjacent carbon atoms (*e.g.* such acids as succinic, maleic, and phthalic) react with ammonia and amines according to the following scheme :



$$\begin{array}{l}-\overset{|}{C}-CO\\ \;\;|\qquad >O\\ -\underset{|}{C}-CO\end{array} + RNH_2 \longrightarrow \begin{array}{l}-\overset{|}{C}-CO_2H\\ \;\;|\\ -\underset{|}{C}-CO{\cdot}NHR.\end{array}$$

This reaction is employed for the characterisation of the anhydrides of these acids (Anschütz, *Ber.*, 1887, **20**, 3214; 1888, **21**, 88; *Annalen*, 1890, **259**, 137; Auwers, *ibid.*, 1895, **285**, 225).

For this purpose a small amount of the anhydride is dissolved in benzene and the solution divided into three parts. To one portion is added aniline, a solution of *p*-toluidine in benzene to the second part, and a solution of naphthylamine to the third. The anilic acids which separate are collected by filtration, washed with a little benzene, and recrystallised. They may be characterised further by heating them above their melting point, when they are converted into anils (Auwers, Oswald, and Thorpe, *Annalen*, 1895, **235**, 229).

It is known that some esters, such as the alkyl oxalates, give an immediate precipitate of the amide when treated with concentrated aqueous ammonia. Although this reaction does not generally proceed so easily with the majority of esters, it can nevertheless be employed as a fairly general method of preparation if the experimental conditions are modified. Thus the methyl esters of *n*-butyric acid and its immediate homologues give the corresponding amides in fairly good yield by agitation with concentrated aqueous ammonia at room temperature for 12—30 hours. If the amides are soluble in water, they can be isolated from the product by extraction with chloroform. The reaction of the higher homologues with aqueous ammonia is much slower and not very satisfactory. The amides of some aromatic acids may be obtained by a similar process (H. Meyer, *Monatsh.*, 1906, **27**, 31).

An alternative process for esters which do not easily furnish amides by reaction with cold aqueous ammonia is to heat them with alcoholic ammonia in sealed tubes at 100—150° (A. W. Hofmann, *Ber.*, 1882, **15**, 977), or to keep a solution of the ester in alcohol saturated with ammonia.

In the formation of amides from esters some interesting anomalies have been recorded. While malonic ester readily gives a diamide by treatment with aqueous or alcoholic ammonia, the dialkylmalonic esters are extraordinarily stable when thus treated. Thus the dimethyl ester of diethylmalonic acid is not attacked by an excess of concentrated ammonia at room temperature after 30 hours, and scarcely at all by heating at 140—150° for 12 hours with alcoholic ammonia. The esters of dimethyl- and dipropyl-malonic acids furnish very little amide by heating with alcoholic ammonia (E. Fischer and Dilthey, *Ber.*, 1902, **35**, 844; compare H. Meyer, *loc. cit.*).

This type of preparation has been used successfully for the preparation of a number of hydrazides, by using hydrazine hydrate in place of ammonia.

Preparation of Benzahydrazide.—Hydrazine hydrate (1½ mol. props.) in a round-bottomed flask fitted with a reflux condenser is heated on a steam-bath. Ethyl benzoate (1 mol. prop.) is gradually added, the addition of fresh portions being delayed till the previous portion has dissolved. The reaction mixture is heated for some hours on the water-bath after all the ester has been added. A white crystalline mass separates on cooling. It is removed from the flask, the lumps are broken up and drained at the pump. Finally it is washed successively with small amounts of alcohol and ether.

The filtrates after concentration yield, by further heating under reflux, more of the hydrazide.

The product is purified by crystallisation from boiling water, m. p. 112—113° (Curtius and Struve, *J. pr. Chem.*, 1895, [ii], **50**, 295).

This method has been applied to the preparation of hydrazides of many of the saturated fatty acids, some substituted benzoic acids, malonic and oxalic acids, and also of some hydroxy-acids such as glycollic acid (Curtius and his co-workers, *J. pr. Chem.*, 1895, [ii], **51**, 165, 180, 353; 1901, [ii], **64**, 401, 419).

In the same way, hydroxamic acids (of the general formula $R{\cdot}CO{\cdot}NHOH$ or $R{\cdot}C(OH){:}NOH$) may be prepared by treating esters with free hydroxylamine

$$R{\cdot}CO{\cdot}OEt + NH_2OH \longrightarrow R{\cdot}CO{\cdot}NHOH + EtOH$$

Preparation of Formhydroxamic Acid.—A solution of hydroxylamine in methyl alcohol is prepared by the addition of the calculated amount of sodium methoxide in methyl alcohol to hydroxylamine hydrochloride.

The calculated amount of this solution is mixed with the necessary amount of ethyl formate. After keeping for 24 hours, the alcohol is removed by evaporation under reduced pressure. The residue consists of formhydroxamic acid, white shining platelets, m. p. 72—74° (Schroeter, *Ber.*, 1898, **31**, 2191).

An exchange of the amino-group in amides may sometimes be effected by heating with a comparatively non-volatile amine, although the method is, in general, of limited application (compare Herd, Dull, and Martin, *J. Amer. Chem. Soc.*, 1932, **54**, 1974).

$$R{\cdot}CONH_2 + R{\cdot}NH_2 \longrightarrow R{\cdot}CONHR + NH_3$$

It has nevertheless been employed as an alternative process for the preparation of hydrazides and hydroxamic acids.

Preparation of Benzhydrazide from Benzamide.—Equivalent amounts of benzamide and hydrazine hydrate in 3 parts of water are heated under reflux till no more ammonia is evolved. The hydrazide is collected by filtration (Curtius and Struve, *loc. cit.*).

C. Hoffmann (*Ber.*, 1889, **22**, 2854) describes the preparation of benzhydroxamic acid by heating benzamide with free hydroxylamine.

Acethydroxamic acid has been obtained by keeping acetamide and hydroxylamine hydrochloride together in concentrated solution till the latter no longer reduces Fehling's solution. The hydroxamic acid is isolated by precipitation as its copper salt.

(e) *Formation of Esters.*

The esterification of carboxylic acids by alcohols has already been considered on pp. 81–83. From the many series of investigations of the rate of esterification under the influence of catalysts, it is clear that the constitution of the acid has an effect on the ease of ester formation. Generally speaking, substituents of saturated fatty acids in the α-position retard esterification to some extent (Sudborough and Gittins, *J.*, 1908, **93**, 210; Sudborough and M. K. Turner, *ibid.*, 1912, **101**, 237; E. R. Thomas and Sudborough, *ibid.*, p. 317; Sudborough, *ibid.*, p. 1227). Monobasic aromatic acids with a substituent in the *ortho* position to the carboxyl have generally lower rates of esterification than the isomeric *meta-* and *para-*substituted acids. This effect is enhanced if both *ortho* positions are occupied. The extent of the retardation depends largely on the nature of the substituents, nitro- and halogen groups being more effective than hydroxyl or methyl. Thus 2 : 6-dichloro- or 2 : 6-dinitro-benzoic acid is scarcely esterified by boiling alcoholic hydrogen chloride, while tetrahalogen-substituted *tere-* and *iso*-phthalic acids are not esterified at all under these conditions. Further details regarding this can be obtained by consulting the original papers (V. Meyer and Sudborough, *Ber.*, 1894, **27**, 1580, 3146. Meyer, *ibid.*, p. 510; 1895, **28**, 182, 1254, 3197; 1896, **29**, 831, 1399; V. Meyer and L. Wöhler, *ibid.*, p. 2569; Rupp, *ibid.*, 1896, **29**, 1625; Meyer and Kellas, *Z. phys. Chem.*, 1897, **24**, 219, 221; Meyer and Molz, *Ber.*, 1898, **30**, 1277).

The retardation of the esterification is explained on the assumption that an accumulation of groups adjacent to the carboxyl prevents free access of the alcohol to the carboxyl. This view appears to be supported by the fact that if a di-*ortho*-substituted benzoic acid is compared with one having the same aromatic nucleus but with a $-CH_2$ interposed between the carboxyl and the nucleus, there is no such retardation during its esterification. Probably other factors are also involved (compare v. Auwers and Harres, *Z. phys. Chem.*, 1929, **143**, 17).

When direct esterification of acids by alcohols is neither applicable nor convenient for preparative purposes, other methods are available. For instance, resort may be made to the action of acyl chlorides or anhydrides on hydroxylic compounds. This is a method for preparing phenyl esters, and is frequently used for the characterisation of small amounts of alcohols and also of acids (see pp. 78–80). The reaction between alkyl halides and the salts of acids according to the following scheme :

$$R{\cdot}CO_2Ag + ICH_3 \qquad R{\cdot}CO{\cdot}OCH_3 + AgI$$

also furnishes esters. The method is limited, however, by the ease with which the alkyl halide tends to eliminate the element of halogen hydride forming the corresponding olefin (see p. 382). Nevertheless, it is used extensively for the conversion of dibromo-paraffins into the corresponding esters, and thence by hydrolysis into glycols when the usual methods of heating the bromo-compounds with aqueous alkali do not give satisfactory yields of the glycol. It is also applied to the preparation of methyl and ethyl esters of those substituted benzoic acids which are not readily esterified by the normal method. It has been employed comparatively recently for the characterisation of carboxylic acids by converting them into crystalline esters by reaction of their salts with substituted benzyl halides or nuclear-substituted ω-halogen acetophenones. This has been largely due to Reid and his co-workers, who have worked out standard conditions for this reaction.

Preparation of p-*Nitrobenzyl Esters.*—A solution of 0·5 g. of *p*-nitrobenzyl bromide in 5 c.c. of 95% alcohol is added to slightly more than the calculated amount of the sodium salt of the acid in 2·5 c.c. of water. The mixture is heated under reflux for 1 hour for a monobasic acid, or 2 hours for a dibasic acid. The ester may separate on cooling; if not, water is added gradually. The solid ester is purified by crystallisation from alcohol (E. E. Reid, *J. Amer. Chem. Soc.*, 1917, **39**, 124, 107).

If the nitrobenzyl ester is not satisfactory for the characterisation of the acid, nuclear-substituted ω-bromoacetophenones may be used instead of *p*-nitrobenzyl bromide (Judefind and Reid, *J. Amer. Chem. Soc.*, 1920, **42**, 1043; Hann, Reid, and Jamieson, *ibid.*, 1930, **52**, 818).

Methyl esters of carboxylic acids may also be prepared by the action of diazomethane on the free acid (v. Pechmann, *Ber.*, 1895, **28**, 856).

(f) *Preparation of Aldehydes and Ketones from Acids.*

It has been known for some time that some salts of the monobasic acids yield ketones by dry distillation (Péligot, *Annalen*, 1834, **12**, 40), the calcium and barium salts being generally employed.

$$(R{\cdot}CO{\cdot}O)_2Ca \longrightarrow R_2CO + CaCO_3$$

This process is used for the technical production of acetone by the distillation of calcium acetate. The salts of the higher homologues of acetic acid and those of many aromatic acids behave similarly.

The reaction has been extended to the preparation of aldehydes and of mixed ketones. Aldehydes are formed by the dry distillation of an intimate mixture of calcium or barium formate with the corresponding salt of a suitable monobasic acid.

$$(R{\cdot}CO_2)_2Ca + (H{\cdot}CO_2)_2Ca \longrightarrow 2R{\cdot}CHO + 2CaCO_3$$

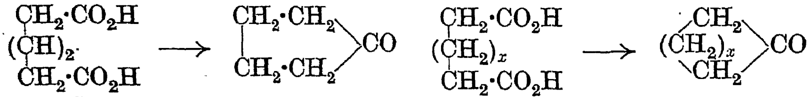
Similarly, mixed ketones are obtained by replacing the calcium formate by the calcium salt of another acid.

$$(R{\cdot}CO_2)_2Ca + (R'{\cdot}CO_2)_2Ca \longrightarrow 2R{\cdot}CO{\cdot}R' + 2CaCO_3$$

Such methods are, however, generally inconvenient and usually give poor yields, but are nevertheless employed in special circumstances (compare Morgan and Holmes, *J.S.C.I.*, 1925, **44**, 108T, 491T).

A more satisfactory process for the preparation of ketones is the catalytic method of Senderens (*Compt. rend.*, 1909, **148**, 927; **149**, 213, 995), in which the fatty acid or mixture of fatty acids is passed through a tube containing thorium oxide heated to 400°. The yields of ketones of the type $R{\cdot}CO{\cdot}CH_3$ ($R =$ alkyl) obtained by this method are about 70—90% of theory (Pickard and Kenyon, *J.*, 1911, **99**, 56; 1912, **101**, 628; 1913, **103**, 1936).

Dibasic acids of suitable structure may be converted into cyclic ketones. Thus ketopentamethylene (II) is obtained by the dry distillation of the calcium salt of adipic acid (I). The calcium salts of suberic, pimelic, and azelaic acids behave similarly, but the yield of ketone depends on the number of $-CH_2$ groups present.



$$\begin{array}{l} CH_2{\cdot}CO_2H \\ (CH)_2 \\ CH_2{\cdot}CO_2H \end{array} \longrightarrow \begin{array}{l} CH_2{\cdot}CH_2 \\ | \\ CH_2{\cdot}CH_2 \end{array}\!\!>CO \qquad \begin{array}{l} CH_2{\cdot}CO_2H \\ (CH_2)_x \\ CH_2{\cdot}CO_2H \end{array} \longrightarrow (CH_2)_x\begin{array}{l} CH_2 \\ \\ CH_2 \end{array}\!\!>CO$$

(I.) (II.)

(Hentzschel and J. Wislicenus, *Annalen*, 1893, **275**, 312; Wislicenus and co-workers, *ibid.*, pp. 341, 351, 356).

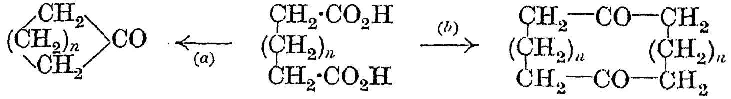
Among the variations of this method which have been employed are distillation of the dibasic acid with iron filings or with salts of nickel, iron, cobalt, manganese or other catalysts (Farbenfabrik vorm. F. Bayer and Co., D.R.-P. 256,622); slow distillation of the acid with acetic anhydride (Blanc, *Compt. rend.*, 1907, **144**, 1356; *Bull. Soc. chim.*, 1908, [iv], **3**, 778, 780); slow distillation of the acid in a stream of carbon dioxide (Aschan, *Ber.*, 1912, **45**, 1605).

Recently the preparation of cyclic ketones by the dry distillation of salts of dibasic acids other than those of the alkaline earths has received considerable attention. In particular, thorium, cerium, and yttrium salts have been used with good results. The following table shows how the yield of ketone is dependent on the acid and on the experimental conditions.

Acid.	Salt used and yield of ketone.						Free acid.
	Ca.	Th.	Ce‴.	Zr.	Pb.	Fe.	
Glutaric	0	0	—	—	—	<1	0
Adipic	45	15	—	—	—	51	80
Pimelic	40—50	70	—	—	—	56	52
Suberic	35	50	45	—	2—3	40	<2
Azelaic	5	20	10	2	2	10	<1
Sebacic	<1	1·5	—	—	—	<1	<1

(Ruzicka, Brugger, M. Pfeiffer, Schinz, and Stoll, *Helv. Chim. Acta*, 1926, **9**, 499; Vogel, *J.*, 1928, 2032.)

The distillation of salts of dibasic acids has been extended by Ruzicka and his co-workers to the preparation of a series of cyclic ketones containing 9—30 carbon atoms (*Helv. Chim. Acta*, 1926, **9**, 249, 399, 499; 1928, **11**, 496, 670, 686). The process of cyclisation appears to occur in two directions: (*a*) the formation of a mono-ketone; (*b*) formation of a diketone by condensation of 2 molecules of acid. The diketone is formed in relatively small amount (Ruzicka, Stoll, Huyser, and Boekenoogen, *Helv. Chim. Acta*, 1930, **13**, 1152).



$$(CH_2)_n\!\left\langle{CH_2 \atop CH_2}\right\rangle\!CO \xleftarrow{(a)} \begin{array}{l} CH_2\cdot CO_2H \\ (CH_2)_n \\ CH_2\cdot CO_2H \end{array} \xrightarrow{(b)} \begin{array}{lcl} CH_2 & -CO- & CH_2 \\ (CH_2)_n & & (CH_2)_n \\ CH_2 & -CO- & CH_2 \end{array}$$

The formation of cyclic ketones is accompanied by formation of saturated monobasic acids (Aschan, *loc. cit.*; Vogel, *loc. cit.*), and according to Aschan by some unsaturated acid also.

From some dibasic acids abnormal products result. Thus the thorium salt of azelaic acid yields on dry distillation *cyclo*-octanone as the main product with small amounts of *cyclo*hexanone besides (Ruzicka and Brugger, *Helv. Chim. Acta*, 1926, **9**, 399; compare Day, Kon, and Stevenson, *J.*, 1920, **117**, 642). In this connection it should be noted that in the preparation of open-chain ketones by dry distillation of the calcium salts of monobasic acids several observations of the formation of abnormal products are recorded. Thus methyl ethyl ketone is reported as a minor product of the dry distillation of calcium acetate (Nef, *Annalen,* 1900, **310**, 333; compare Friedel, *ibid.*, 1858, **108**, 125; Grimm, *ibid.*, 1871, **157**, 253).

(g) *Behaviour of Acids and their Salts on Electrolysis.*

Kolbe (*Annalen,* 1849, **69**, 279) reported that concentrated solutions of sodium acetate yield ethane and carbon dioxide on electrolysis. It has since been recognised that small amounts of other products are formed such as hydrogen and ethylene (Kempf and Kolbe, *J. pr. Chem.*, 1871, [ii], **4**, 46) or methyl alcohol (Hofer and Moest, *Z. Elektrochem.*, 1904, **10**, 833).

Investigations of the behaviour on electrolysis of salts of the homologues of acetic acid have shown that the usual products are a mixture of olefin and paraffin, ester and alcohol (compare Petersen, *Z. phys. Chem.*, 1900, **33**, 108, 295). Thus potassium valerate yields *n*-octane, *n*-butyl valerate, butylene, and hydrogen. Potassium caproate yields chiefly *n*-decane with small amounts of amyl alcohol, amyl caproate, and amylene. The principal product of the electrolysis of trichloroacetic acid is the trichloroacetate of trichloromethyl alcohol (Elbs and Kratz, *J. pr. Chem.*, 1897, [ii], **55**, 502).

The formation of these different types of products has been explained either by the union of discharged anions (Scheme *b*) (Crum Brown and J. Walker, *Annalen,* 1891, **261**, 107) or by direct oxidation (Scheme *a*) (compare R. E. Gibson, *J.*, 1925, **127**, 475). The oxidation hypothesis appears to be the more likely.

$$\mathrm{R{\cdot}CO{\cdot}OH + R{\cdot}CO{\cdot}OH + O \longrightarrow R{\cdot}R + 2CO_2 + H_2O}$$
$$\longrightarrow \mathrm{R{\cdot}CO{\cdot}OR + CO_2 + H_2O} \qquad \text{Scheme } a$$
$$\mathrm{R{\cdot}CO{\cdot}OH + O \longrightarrow R{\cdot}OH + CO_2}$$

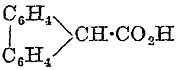
$$\mathrm{2R{\cdot}CO_2{}' \longrightarrow R{\cdot}R + CO_2}$$
$$\searrow \mathrm{R{\cdot}CO{\cdot}OR + CO_2} \qquad \text{Scheme } b$$
$$\mathrm{R{\cdot}CO_2{}' + OH' \longrightarrow R{\cdot}OH + CO_2}$$

A more satisfactory application of electrosynthesis is to be found in the formation of the esters of dibasic acids by the electrolysis of acid esters of dibasic acids (Crum Brown and J. Walker, *Annalen,* 1891, **261**, 107; 1893, **274**, 41)

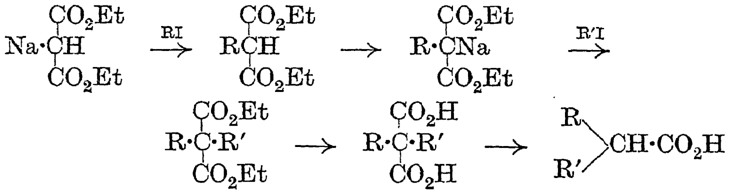
$$\mathrm{2\ Alk{\cdot}O_2C{\cdot}(CH_2)_x{\cdot}CO_2{}' \longrightarrow Alk{\cdot}O_2C{\cdot}(CH_2)_x{\cdot}(CH_2)_x{\cdot}CO_2{\cdot}Alk + 2CO_2}$$

(h) *Elimination of Carbon Dioxide from Carboxylic Acids.*

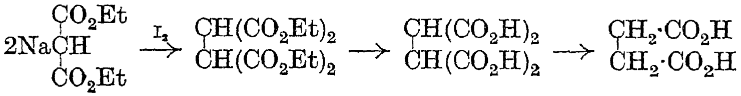
Monobasic carboxylic acids such as the saturated and unsubstituted aliphatic acids or benzoic acid and its homologues are comparatively stable and do not easily yield carbon dioxide on heating. The presence of negative substituents such as $-NO_2$, $-CO_2H$, and to a less extent phenyl, in the fatty acids generally reduces the stability. The effect is most pronounced if the substituent occupies the α-position with respect to the carboxyl. The general effect is illustrated by the following examples.

$CH_3{\cdot}CO_2H$	Unchanged at 390°.	Engler and Löw, *Ber.*, 1893, **26**, 1436.
$\begin{array}{l}CO_2H\\ \vert\\ CH_2\\ \vert\\ CO_2H\end{array}$	Loses CO_2 and converted into acetic acid at its melting point.	
$\begin{array}{l}CH_2{\cdot}CO_2H\\ \vert\\ CH_2{\cdot}CO_2H\end{array}$	Yields anhydride on distillation.	
$NO_2{\cdot}CH_2{\cdot}CO_2H$	Moist acid slowly loses CO_2 at room temperature to form $CH_3{\cdot}NO_2$.	Steinkopf, *Ber.*, 1909, **42**, 3925.
$Ph{\cdot}CH_2CO_2H$	After several hours at 350—375°, 75% converted into toluene.	Engler and Löw, *loc. cit.*
$Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	Only slightly changed at 370°.	Engler and Löw, *loc. cit.*
	Yields CO_2 and fluorene at about 220—230°.	W. Wislicenus and Ruthing, *Ber.*, 1913, **46**, 2771.

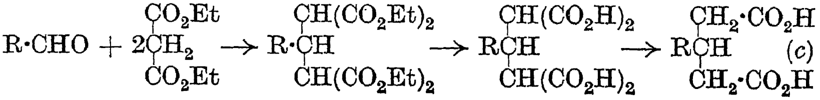
The ready elimination of carbon dioxide from some classes of α-substituted fatty acids is frequently utilised for syntheses or in preparative work. One of the most important of such applications is to be found in the malonic acid synthesis. This method is available for the preparation of unsaturated monobasic acids by the condensation of an aldehyde with malonic acid (p. 147); glutaric acid and its β-substituted products by condensation of malonic esters with formaldehyde and other aliphatic aldehydes under suitable conditions (equations *c*) (p. 149); the formation of monobasic fatty acids by reaction of the sodium salt of diethyl malonate with alkyl halides (equation *a*); the formation of succinic acid and its alkyl-substituted products from the action of iodine on the sodium derivatives of malonic esters (equation *b*). These are represented by the following schemes :



$$\mathrm{Na{\cdot}}\begin{array}{c}CO_2Et\\ \vert\\ CH\\ \vert\\ CO_2Et\end{array} \xrightarrow{RI} \mathrm{R}\begin{array}{c}CO_2Et\\ \vert\\ CH\\ \vert\\ CO_2Et\end{array} \longrightarrow \mathrm{R{\cdot}}\begin{array}{c}CO_2Et\\ \vert\\ CNa\\ \vert\\ CO_2Et\end{array} \xrightarrow{R'I} \mathrm{R{\cdot}}\begin{array}{c}CO_2Et\\ \vert\\ C\\ \vert\\ CO_2Et\end{array}\mathrm{{\cdot}R'} \longrightarrow \mathrm{R{\cdot}}\begin{array}{c}CO_2H\\ \vert\\ C\\ \vert\\ CO_2H\end{array}\mathrm{{\cdot}R'} \longrightarrow \begin{array}{l}R\diagdown\\ \\ R'\diagup\end{array}\!\!\mathrm{CH{\cdot}CO_2H} \qquad (a)$$



$$2\mathrm{Na}\begin{array}{c}CO_2Et\\ \vert\\ CH\\ \vert\\ CO_2Et\end{array} \xrightarrow{I_2} \begin{array}{l}CH(CO_2Et)_2\\ \vert\\ CH(CO_2Et)_2\end{array} \longrightarrow \begin{array}{l}CH(CO_2H)_2\\ \vert\\ CH(CO_2H)_2\end{array} \longrightarrow \begin{array}{l}CH_2{\cdot}CO_2H\\ \vert\\ CH_2{\cdot}CO_2H\end{array} \qquad (b)$$



$$\mathrm{R{\cdot}CHO} + 2\begin{array}{c}CO_2Et\\ \vert\\ CH_2\\ \vert\\ CO_2Et\end{array} \longrightarrow \mathrm{R{\cdot}}\begin{array}{l}CH(CO_2Et)_2\\ \vert\\ CH\\ \vert\\ CH(CO_2Et)_2\end{array} \longrightarrow \mathrm{R}\begin{array}{l}CH(CO_2H)_2\\ \vert\\ CH\\ \vert\\ CH(CO_2H)_2\end{array} \longrightarrow \mathrm{R}\begin{array}{l}CH_2{\cdot}CO_2H\\ \vert\\ CH\\ \vert\\ CH_2{\cdot}CO_2H\end{array} \qquad (c)$$

The decarboxylation of these acids is effected by heating above their melting point.

An analogous behaviour of cinnamic acid is used for the preparation of styrene. The decomposition is, however, slower than that of malonic acid.

Preparation of Styrene.—Cinnamic acid (148 g.) mixed with 2 g. of quinol and some pieces of porous tile is slowly distilled through a fractionating column, so that the temperature of the vapour at the head of the column never exceeds 130° and is mainly below 120°. Styrene distils over and is collected in a cooled receiver containing about ½ g. of quinol.

When no more styrene passes over, the distillate is mixed with water and distilled. The styrene which is obtained in the distillate is separated from the water, dried over calcium chloride, and distilled under reduced pressure, b. p. 44—46°/40 mm.—yield 40—42 g.

The fractionating column recommended by the authors is 24 cm. long from the side arm to the lower end and has an internal diameter of 13—14 mm. (Abbot and J. R. Johnson, *Organic Syntheses*, 1928, **8**, 85).

Many acids lose carbon dioxide comparatively readily by heating either aqueous solutions of the free acid or its salts. Thus α-nitroacetic acid is very sensitive to traces of moisture, yielding nitromethane and carbon dioxide; the rate of decomposition increases on warming. This ready elimination of carbon dioxide is no doubt the basis of Kolbe's method of preparing nitromethane, in which an aqueous solution of a salt of chloro- or bromo-acetic acid is heated with a solution of sodium nitrite to replace the halogen (Kolbe, *J. pr. Chem.*, 1872, [ii], **5**, 427; Preibisch, *ibid.*, 1874, [ii], **8**, 310).

$$CH_2Cl{\cdot}CO_2Na + NaNO_2 \longrightarrow CH_2(NO_2){\cdot}CO_2Na \xrightarrow{H_2O} CH_3{\cdot}NO_2 + NaHCO_3$$

This method has been extended to the preparation of homologues of nitromethane by using the appropriate α-halogen-substituted fatty acid instead of chloroacetic acid. The yield of nitro-compound, however, diminishes as the series is ascended, and the method is of little practical importance beyond the sixth or seventh member of the series (compare Auger, *Bull. Soc. chim.*, 1900, [iii], **23**, 333).

Preparation of Nitromethane.—A solution of 94·5 g. of chloroacetic acid in 100 c.c. of ice-water is neutralised in a 750-c.c. distillation flask by the cautious addition of about 70 c.c. of cold 40% sodium hydroxide solution. The temperature should be kept below 20° and the addition of alkali continued till the solution is faintly alkaline to phenolphthalein. A solution of 74 g. of sodium nitrite in 100 c.c. of water is now added and the mixture gradually warmed till bubbles of carbon dioxide appear. The heating is now stopped and the reaction allowed to proceed by itself. During this stage some nitromethane and water distil over. When the reaction moderates, the heating is continued and the remainder of the nitromethane distilled over, till the volume of the distillate is about 110 c.c. The nitromethane in the distillate is separated from the aqueous layer, which is mixed with salt and again distilled till about a quarter of its bulk has been collected. This furnishes a further quantity of nitromethane.

The nitromethane is dried over calcium chloride and distilled, b. p. 98—101°—yield about 35% of theory (F. C. and M. G. Whitmore, *Organic Syntheses*, 1923, 3, 83).

There are several recorded examples of acids losing carbon dioxide more readily in aqueous solution than in the dry state. The decarboxylation under these conditions is usually favoured by the presence of weakly alkaline solutions. Thus fluorene-9-carboxylic acid, which in the dry state loses carbon dioxide when fused (210—220°), is smoothly converted into fluorene by boiling its solution in dilute alkali. An interesting case of the elimination of carbon dioxide is the formation of ω-bromostyrene by heating αβ-dibromo-β-phenylpropionic acid with water or dilute aqueous alkali (Fittig and Binder, *Annalen*, 1879, **195**, 141; Nef, *ibid.*, 1899, **308**, 267).

$$\mathrm{Ph{\cdot}CHBr{\cdot}CHBr{\cdot}CO_2H \longrightarrow Ph{\cdot}CH{:}CHBr + CO_2 + HBr}$$

Apparently the removal of the carbon dioxide occurs simultaneously with the removal of the elements of hydrogen bromide (Sudborough and Thompson, *J.*, 1903, **83**, 681). Although αβ-dibromo-β-phenylpropionic acid yields ω-bromostyrene, it is curious that α-bromocinnamic acid does not lose carbon dioxide so readily.

Further examples of the concurrent elimination of halogen hydride and carbon dioxide are seen in the formation of styrene by boiling β-phenyl-β-bromopropionic acid or the corresponding iodo-compound with water or dilute sodium carbonate solution (Fittig and Binder, *loc. cit.*); or in the formation of butylene from α-methyl-β-iodobutyric acid by warming with aqueous sodium carbonate (J. Wislicenus, Talbot, and Henze, *Annalen*, 1900, **313**, 228).

Preparation of ω-Bromostyrene.—Cinnamic acid dibromide (200 g.) is heated with 1140 c.c. of 10% sodium carbonate solution under reflux. ω-Bromostyrene soon commences to separate, and when the reaction is complete, the ω-bromostyrene is removed and dried. It can then be used directly for the preparation of phenylacetylene (Nef, *Annalen*, 1899, **308**, 267).

The ease with which nuclear-substituted benzoic acids are decarboxylated depends on the nature of the substituent groups and their orientation with respect to the carboxyl. If the hydroxyl groups are *ortho* or *para* to the carboxyl, they have a marked influence. Thus salicylic and *p*-hydroxybenzoic acids are partially resolved into phenol and carbon dioxide by heating above their melting point, or by heating with aniline. *m*-Hydroxybenzoic acid, on the other hand, is stable on heating. 2 : 4-Dihydroxybenzoic acid is largely converted into resorcinol by boiling its dilute aqueous solution for about an hour. Phloroglucin carboxylic acid is almost entirely decomposed by boiling its dilute aqueous solution for ½ hour (Hemmelmayr, *Monatsh.*, 1913, **34**, 365). Gallic acid is easily converted into pyrogallol on heating.

Amino-groups in the nucleus also lower the stability of the carboxyl. It is noteworthy that the bromobenzoic acids do not show any marked tendency to lose carbon dioxide. Mono- and di-nitrobenzoic acids are also comparatively stable, although 2 : 4 : 6-trinitrobenzoic acid readily furnishes trinitrobenzoic ~~acid~~ on heating aqueous solutions of its salts. benzene.

Preparation of 1 : 3 : 5-*Trinitrobenzene*.—Crude 2 : 4 : 6-trinitrobenzoic acid (46 g.) is mechanically stirred with 400 c.c. of water at 35° and a 15% solution of sodium hydroxide added till a faint red colour is produced.* After discharging the colour by the addition of a drop of acetic acid, the liquid is filtered and the filtrate mixed with 15 c.c. of glacial acetic acid, and gently heated while it is mechanically stirred. Trinitrobenzene commences to separate as a frothy layer, and it is advisable, if the evolution of carbon dioxide becomes too vigorous, to regulate the heating. When the evolution of carbon dioxide ceases, heating and stirring are continued till the solution contains no more trinitrobenzoate. This is easily ascertained by filtering a portion of the solution and adding dilute sulphuric acid to the filtrate. If no precipitate is formed, the reaction is complete.

The crude trinitrobenzene is then filtered off and crystallised from glacial acetic acid, m. p. 121—122°—yield about 28—30 g. (Clarke and Hartman, *Organic Syntheses*, 1922, **2**, 93).

Those acids which lose carbon dioxide comparatively readily can be decarboxylated conveniently by heating with amines such as pyridine, aniline, quinoline, or dimethylaniline. Thus benzalmalonic acid mixed with pyridine or quinoline eliminates carbon dioxide at room temperature to furnish the amine salts of cinnamic acid (Staudinger, *Ber*., 1906, **39**, 3067 *footnote*). Phenolcarboxylic acids are converted into the corresponding phenols by heating with quinoline or pyridine. *m*-Hydroxybenzoic acid is, however, stable under these conditions (Claisen, *Annalen*, 1918, **418**, 76 *footnote*, p. 80; compare Hemmelmayr, *loc. cit.*).

When this method fails, decarboxylation can be generally achieved by heating an intimate mixture of the acid and an excess of powdered soda lime.

(2) *Special Reactions of the Commoner Groups of Acids.*

(a) *Fatty Acids.*

The physical properties of members of this series show a regular change as the series is ascended. The alteration in melting point and boiling point is seen in Table XII. (p. 254). The change in odour is very pronounced, the lowest members of the series having sharp pungent odours. The odour of formic acid is similar to that of sulphur dioxide, while butyric and valeric acids and their immediate homologues have rancid persistent odours which are extremely disagreeable; lauric acid and the higher acids are, however, almost odourless.

The solubility of these acids in water diminishes with increasing molecular weight, and similar gradations in solubility are found in their salts. While the alkali salts of formic and acetic acid are crystalline solids readily soluble in water, the corresponding salts of palmitic, stearic, and myristic acids are soaps. Salts of the higher fatty acids with other metals have abnormal solubilities.

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* The temperature should be kept below 45° during neutralisation, otherwise decomposition of the acid occurs.

The reactions of formic acid are exceptional in that it is oxidised by ammoniacal solutions of silver nitrate; by aqueous mercuric chloride with the production of mercurous chloride and of mercury; and by permanganate. Concentrated sulphuric acid converts it into carbon monoxide. The other members of the series do not show these reactions, being stable to warm concentrated sulphuric acid and not sensibly attacked by permanganate or cold dilute chromic acid.

Substitution in the alkyl grouping takes place comparatively easily by the action of bromine or chlorine. When the substitution is regulated to give monohalogen-substituted acids, the product is exclusively an α-halogen-substituted acid or acid halide. The importance of this reaction lies in the fact that it furnishes starting points for the preparation of other α-substituted fatty acids by replacement of the halogen. It is moreover used in the stepwise degradation of the fatty acids, the halogen-substituted acid being converted into the corresponding α-hydroxy-acid, and thence, by oxidation, into a fatty acid containing one carbon atom less.

Preparation of α-Bromopalmitic Acid.—Dry bromine (45 g.) is added cautiously to a mixture of palmitic acid (100 g.) and red phosphorus. Heat is evolved and care is necessary during the bromination. When all the bromine has been added, the reaction mixture is heated on a water-bath for about 6 hours and then kept at room temperature overnight. The product is bromopalmityl bromide. It is poured into water and the mixture heated on the water-bath for a short time and then kept for some hours at room temperature. Crude bromopalmitic acid is obtained as a solid which is purified by washing with water, then melting with water, and finally dissolving in ether, filtering, and drying. Evaporation of the solvent leaves almost pure bromopalmitic acid, m. p. 51—52°—yield 125 g.

α-Bromopentadecylic and α-bromomyristic acids are prepared similarly (Le Sueur, *J.*, 1905, **87**, 1895; compare Hell and Sadomski, *Ber.*, 1891, **24**, 2390; Volhard, *Annalen*, 1887, **242**, 141).

The use of phosphorus is not essential in the bromination, for Lapworth (*J.*, 1904, **85**, 41) has found that pure dry acetic acid saturated with dry hydrogen chloride is readily attacked by bromine to yield bromoacetic acid (compare Ward, *J.*, 1922, **121**, 1161). It has been suggested that the bromination is dependent on the conversion of the acid or its bromide into an enolic modification (compare Aschan, *Ber.*, 1913, **46**, 2162; 1912, **45**, 1913). For purposes of preparation it is, however, more convenient to use a small quantity of red phosphorus in the bromination (about 1—2% is sufficient) (Ward, *loc. cit.*).

Preparation of α-Bromoacetic Acid.—Bromine (dried in contact with concentrated sulphuric acid) (58 g.) is added from a tap funnel to dry acetic acid (20 g.) in which is suspended 0·4 g. of dry red phosphorus. The mixture is then heated under reflux in an oil-bath at 100—105° till all the bromine has reacted. The product, which solidifies on cooling, is distilled. The main bulk of the bromoacetic acid is collected at 203° after a small amount of bromoacetyl bromide and unchanged acetic acid have passed over in the first runnings (Ward, *loc. cit.*).

Preparation of a-Bromocaproic Acid.—200 G. of freshly distilled and dry *n*-caproic acid are mixed with 300 g. of bromine (dried in contact with concentrated sulphuric acid) and about 3 g. of phosphorus trichloride added. The mixture is heated under reflux at about 60—70°. A smooth evolution of hydrogen bromide occurs, and as the reaction slackens, the temperature is gradually raised to 100°. When all the bromine has reacted, the product is distilled under reduced pressure. *a*-Bromo-*n*-caproic acid is collected at 132—140°/15 mm. (H. T. Clarke and Taylor, *Organic Syntheses*, 1924, **4**, 9).

Estimation of the Fatty Acids.—Pure specimens of acids are estimated simply by titration with standard alkali using phenolphthalein as indicator. Acids insoluble in water are best titrated in neutral aqueous alcoholic solution.

Special methods for the estimation of formic acid take advantage of the fact that it is quantitatively oxidised by permanganate in dilute sodium carbonate solution (Rupp, *Zeitsch. anal. Chem.*, 1906, **45**, 687). For other methods of estimation, the following papers should be consulted: Rupp, *Arch. Pharm.*, 1905, **243**, 69; Freyer, *Chem. Zeit.*, 1895, **19**, 1184; Leys, *Chem. News*, 1898, **78**, 245. By a suitable choice of these methods formic acid may be estimated in presence of other acids of the series.

If a mixture of two fatty acids is under examination, an approximately accurate analysis of the composition of the mixture may be made by converting the mixture into salts and subsequently estimating the proportion of metal in the mixture. A very convenient method applicable to fatty acids volatile in steam and miscible with water is due to Duclaux (*Ann. Inst. Pasteur*, 1895, **9**, 269). It has been employed very successfully for the determination of the composition of mixtures of fatty acids in fermentation products and for the estimation of small amounts of impurities in specimens of the lower fatty acids (Reilly, Hickinbottom, Henley, and Thaysen, *Biochem. J.*, 1920, **14**, 237; Lamb, *J. Amer. Chem. Soc.*, 1917, **39**, 731; Richmond, *Analyst*, 1919, **44**, 255). It is an empirical method, and its success depends on careful adherence to the prescribed conditions. Improvements in the process have been described by Reilly and Hickinbottom (*Sci. Proc. Roy. Dublin Soc.*, 1919, **15**, 513; 1920, **16**, 120).

(b) *Aromatic Acids.*

The carboxylic derivatives of benzene and its homologues are in general sparingly soluble in water and have higher melting points than the fatty acids. Their salts with alkali metals are usually crystalline solids, soluble in water, which give sparingly soluble basic salts with ferric salts. The silver salts are generally precipitated by the addition of silver nitrate to neutral solutions.

The acids are stable to cold aqueous permanganate, although acids containing alkyl groups attached to the nucleus suffer oxidation by boiling with alkaline permanganate, the alkyl group being converted into carboxyl as in the oxidation of the homologues of benzene (see p. 34).

Substitution in the nucleus is effected by the usual processes of nitration, halogenation, and sulphonation.

Preparation of m-*Nitrobenzoic Acid*.—An intimate mixture of finely-powdered potassium nitrate (200 g.) and benzoic acid (100 g.) is gradually added to concentrated sulphuric acid (300 g.), which is mechanically stirred. When all the solid has been added, the reaction is completed by gently warming till the separation of the nitrobenzoic acids as an oily layer is complete. After cooling, the acid is collected and freed from mineral acid by washing with water and then melting twice with water.

The product consists of *m*-nitrobenzoic acid with some *o*-nitro-acid. The latter is removed by suspending the crude product in twenty times its weight of boiling water and neutralising with concentrated baryta solution. The barium salt of *m*-nitrobenzoic acid is sparingly soluble and is filtered off. By warming the barium salt with hydrochloric acid, *m*-nitrobenzoic acid is liberated. It may be further purified by crystallisation from hot water, m. p. 141°.

Preparation of 3 : 5-*Dinitrobenzoic Acid*.—Fuming nitric acid (130 g.) is added, in small portions, to a solution of 50 g. of benzoic acid in 500 g. of concentrated sulphuric acid. The mixture is then heated for 8—10 hours on a steam-bath and finally for 1—2 hours on a sand-bath till no more brown fumes are evolved. The nitration mixture is poured into 4—5 l. of ice-water. The precipitate of crude 3 : 5-dinitrobenzoic acid is collected, washed with water, and purified by crystallisation from hot water or alcohol, m. p. 204° (Shukoff, *Ber.*, 1895, **28**, 1800).

Preparation of 6-*Chloro*-3-*nitrobenzoic Acid*.—A mixture of 15 g. of nitric acid (100% concentration) and concentrated sulphuric acid (30 g.) is slowly added to a solution of 30 g. of *o*-chlorobenzoic acid in 100 g. of concentrated sulphuric acid. After keeping overnight, the reaction mixture is poured into ice-water, the precipitated acid collected, washed, and then crystallised from dilute alcohol, m. p. 165° (Rupe, *Ber.*, 1897, **30**, 1099).

Preparation of 3-*Nitrophthalic Acid*.—A mixture of 50 g. of phthalic acid, 75 g. of sulphuric acid, and 75 g. of fuming nitric acid is heated in a water-bath for 2 hours. After cooling, 120 c.c. of water are added and the precipitated acids collected after keeping for 12 hours. The precipitate is drained as completely as possible and then spread on porous tiles.

By crystallisation of the dried acid from water, 3-nitrophthalic acid is obtained pure. A more satisfactory method of purification consists in extracting the crude dried product with ether. The ethereal solutions are evaporated and the residue is crystallised repeatedly from water. The more insoluble fractions are 3-nitrophthalic acid—very pale yellow prisms, m. p. *circa* 207° (dec.).

The aqueous mother-liquors contain a considerable proportion of 4-nitrophthalic acid. This is separated by taking advantage of the fact that on esterification it more readily yields a neutral ester than the 3-nitro-acid.

The aqueous solutions from the crystallisation are evaporated and the solid residue is dried at 100° for 2 hours. It is then dissolved in about 1½ times its weight of dry ethyl alcohol, the solution saturated with hydrogen chloride, and then heated in a water-bath for 3 hours. The resulting solution is poured into water, the oil taken up and washed several times with sodium carbonate solution. The neutral ester of 4-nitrophthalic acid, which remains, gradually solidifies. It is purified by crystallisation from ether and afterwards from alcohol, m. p. 34—35°.

The hydrolysis of the ester is best effected by alcoholic potash, the following proportions—30 g. of ester, 60 g. of absolute alcohol, and 12 g. of potassium hydroxide in 10 c.c. of water—yielding a precipitate of the potassium salt. After draining and washing with alcohol, it is dissolved in water and acidified. The pure acid, m. p. 162°, is precipitated (Miller, *Annalen*, 1881, **208**, 223; compare Bogert and Boroscheck, *J. Amer. Chem. Soc.*, 1901, **23**, 744).

Preparation of 3-*Bromobenzoic Acid*.—A mixture of 7 g. of benzoic acid, 9·5 g. of bromine, and 30 c.c. of water is heated in a sealed tube for about 12 hours at between 130° and 160°. The contents of the tube are filtered, washed with water, and then crystallised from hot water or aqueous alcohol, m. p. 155°—yield about 6—7 g.

Characterisation of the monobasic aromatic acids is usually effected by the preparation of amides or anilides by the methods already indicated. Solid esters derived by reaction of the salts of the acids with nitrobenzyl bromide or substituted ω-bromoacetophenones are also used. Those acids containing alkyl groups may be oxidised by alkaline permanganate and the polybasic acids then characterised by determination of the equivalent weight and by the preparation of suitable derivatives.

Many dibasic acids do not yield satisfactory melting points. Those with the carboxyls in the *ortho* position to each other yield well-defined anhydrides by distillation either alone or with acetic anhydride. With the carboxyls in other positions, the preparation of methyl esters often gives satisfactory results.

Preparation of Dimethyl Ester of iso*Phthalic Acid.*—0·1 G. of *iso*phthalic acid and 0·3 g. of phosphorus pentachloride are heated cautiously over a very small flame till the mixture melts to a clear liquid. It is then cooled and dissolved in 2 c.c. of methyl alcohol. Dimethyl *iso*phthalate is precipitated from the solution by the addition of 5 c.c. of water. The precipitate of the ester is collected by filtration, washed with 2 c.c. of water, and then crystallised from a small quantity of aqueous methyl alcohol, m. p. 64°. Terephthalic acid yields a crystalline dimethyl ester, m. p. 140°, by a similar process (Mulliken, *The Identification of Pure Organic Compounds,* Vol. 1, p. 85).

(c) *Unsaturated Acids.*

Most of the special reactions of unsaturated acids due to the presence of the double bond have been discussed in Chap. I, pp. 4–30. The addition of bromine to the unsaturated linkages of acids is frequently a very slow reaction, and consequently of uncertain value in the recognition of unsaturated acids. A more certain method of detection, which must, of course, be taken in conjunction with other tests, is the reaction with cold dilute neutral aqueous permanganate. Unsaturated acids cause reduction of the permanganate to manganese dioxide.

Unsaturated acids should be characterised as far as possible by methods which establish the presence of unsaturated linkages—such as formation of addition compounds with bromine; oxidation with permanganate, ozone or peracids; hydrogenation. Amides, anilides, or even esters should also be prepared. Higher unsaturated fatty acids are also characterised by their iodine value.

Determination of Iodine Value. Wijs Method.—A stock solution of iodine monochloride is prepared by passing chlorine into a solution of 13 g. of iodine in 1000 c.c. of acetic acid till the original iodine titration has been doubled. The concentration of this solution is determined before each series of iodine value determinations, by adding an excess of potassium iodide to a known volume of the iodine monochloride solution and then titrating the liberated iodine with thiosulphate.

For the determination of the iodine value, a known weight of the fat or acid (0·15—1 g. according to the degree of unsaturation) is dissolved in 10 c.c. of carbon tetrachloride and mixed with a measured volume of iodine monochloride solution. The mixture, which must contain an excess of iodine monochloride solution, is kept in a dark cupboard till the reaction is complete. This may require from ½ hour for iodine values below 100; 1—2 hours for semi-drying oils; 2—6 hours for drying oils.

When the addition is complete, an excess of potassium iodide solution is added, the mixture shaken, diluted with water, and the free iodine determined by titration with thiosulphate.

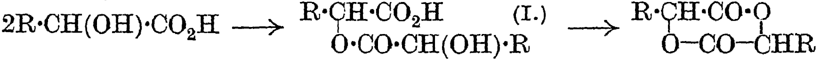
The results are calculated to give the grams of iodine used by 100 g. of the sample, which is the definition of the term "iodine value."

An alternative method is available in which the iodine monochloride solution is replaced by an alcoholic solution of iodine and mercuric chloride.

(d) *Hydroxy-Acids.*

The hydroxy-acids, by virtue of an alcoholic group, react not only as acids, but also as alcohols, for the hydroxyl may be replaced by halogen or may yield acyl derivatives. They exhibit some reactions which are dependent on the position of the hydroxyl with respect to the carboxyl. In the following paragraphs reference is made to the more important characteristics of some of the classes of hydroxy-acids.

1. *α-Hydroxy-Acids.*—These acids suffer two main types of change on heating : (1) esterification of the alcoholic hydroxyl by the carboxyl of another molecule of acid to give a hemilactide (I), and finally a lactide (II). (2) Elimination of the elements of formic acid to yield an aldehyde



$$2\text{R·CH(OH)·CO}_2\text{H} \longrightarrow \begin{matrix}\text{R·CH·CO}_2\text{H}\\ |\\ \text{O·CO·CH(OH)·R}\end{matrix} \quad \text{(I.)} \longrightarrow \begin{matrix}\text{R·CH·CO·O}\\ |\qquad\qquad |\\ \text{O—CO—CHR}\end{matrix}$$

$$\text{R·CH(OH)·CO}_2\text{H} \longrightarrow \text{R·CHO} + \text{HCO}_2\text{H}. \qquad \text{(II.)}$$

These reactions have been examined for acids of the type R·CH(OH)CO$_2$H up to α-hydroxystearic acid, and it appears that they are independent (Le Sueur, *J.*, 1904, **85**, 827; 1905, **87**, 1888; Blaise, *Compt. rend.*, 1904, **138**, 697; *Bull. Soc. chim.*, 1904, [iii], **31**, 483; Bagard, *ibid.*, 1907, [iv], **1**, 307; Pickard and Kenyon, *J.*, 1913, **103**, 1947). Better yields of aldehydes are obtained from α-acyloxy-acids and α-alkoxy-acids.

Preparation of Margaric Aldehyde.—α-Hydroxystearic acid contained in a small flask (15—20 g. is a convenient amount) is maintained at 270—280° for 1 hour (thermometer in the molten acid). The residues from several decompositions are combined and distilled under reduced pressure. The distillate is subjected to several fractional distillations under reduced pressure. Pure margaric aldehyde passes over at 195—210°/26 mm., m. p. 35—36°—yield is approximately 17—18 g. from 40 g. of acid (Le Sueur, *loc. cit.*).

Preparation of Lactide.—Lactic acid is heated at 140—150°, either under reduced pressure or in a slow current of air. A syrup collects in the receiver, which deposits crystals of lactide, m. p. 125° (Wislicenus, *Annalen*, 1872, **164**, 191; 1873, **167**, 319, *footnote*).

Hydroxy-acids of the type $RR'C(OH)\cdot CO_2H$ behave similarly on heating, yielding a ketone instead of an aldehyde. In addition, an unsaturated acid is also formed. For the earlier members of the series (where R and R′ are methyl, ethyl, or propyl) the yield of unsaturated acid increases at the expense of the ketone as the series is ascended (Blaise and Bagard, *Compt. rend.*, 1906, **142**, 1087).

The direct conversion of free α-hydroxy-acids into the corresponding α-keto-acids is rendered difficult owing to the ease with which further oxidation occurs. It has, however, been accomplished by the action of permanganate on neutral aqueous solutions of some α-hydroxy-acids, but the method apparently cannot be applied generally (Beilstein and Wiegand, *Ber.*, 1884, **17**, 840; Heller, *ibid.*, 1911, **44**, 2419; 1913, **46**, 287). A better method of obtaining α-keto-acids from the corresponding α-hydroxy-acids consists in oxidising the esters with permanganate (Aristoff and Demjanoff, *J. Russ. Phys. Chem. Soc.*, 1887, **1**, 257). Oxidation of aqueous solutions of the free α-hydroxy-acids to α-keto-acids can be accomplished by Fenton's reagent—hydrogen peroxide and a trace of a ferrous salt.

Preparation of Pyruvic Acid.—A solution of lactic acid in water is treated with a small amount of ferrous acetate ($\frac{1}{8}$ atomic proportion or less), and cooled in ice. Oxidation is achieved by adding gradually a solution of hydrogen peroxide till about half the calculated amount has been used. It is not advisable to add more oxidising agent in order to minimise its action on the pyruvic acid. The solution must be kept ice cold throughout the oxidation. The addition of phenylhydrazine acetate (equivalent to the hydrogen peroxide used) gives a yellow precipitate of the phenylhydrazone of pyruvic acid, m. p. 192° after crystallisation (Fenton and H. O. Jones, *J.*, 1900, **77**, 71).

This process of oxidation has been applied successfully to the preparation of keto-acids from tartaric, glycollic, and tartronic acids (Fenton, *J.*, 1894, **65**, 899; Fenton and H. O. Jones, *ibid.*, 1900, **77**, 69).

The production of aldehydes constitutes an interesting type of degradation of the α-hydroxy-acids. This may be accomplished, not only by heating (see above), but also by electrolysis of the aqueous solutions of these sodium salts (v. Miller and Hofer, *Ber.*, 1894, **27**, 467; compare Kolbe, *Annalen*, 1860, **113**, 244); by treatment with lead dioxide (Baeyer, *Ber.*, 1897, **30**, 1962; Baeyer and H. v. Liebig, *ibid.*, 1898, **31**, 2106); and also by the action of mercuric oxide on aqueous solutions of the hydroxy-acid (Guerbet, *Bull. Soc. chim.*, 1908, [iv], **3**, 427). This last process has been applied not only for the degradation of lactic and of α-hydroxybutyric acids to acetaldehyde and propaldehyde respectively, but also to the preparation of arabinose from gluconic acid.

By Dakin's method—oxidation of the ammonium salt of the α-hydroxy-acid with warm 3% hydrogen peroxide—the aldehyde results with smaller or greater amounts of acid from the further oxidation of the aldehyde (*J. Biol. Chem.*, 1908, **4**, 91).

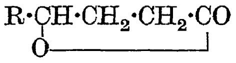
More vigorous oxidation of the α-hydroxy-acids by means of permanganate leads to the elimination of an atom of carbon as carbon dioxide and the formation of a saturated fatty acid. This method is of importance in that it supplies a method of breaking down the fatty acid carbon by carbon, for the α-hydroxy-acids are obtained smoothly from the α-bromo-acids (see p. 371) which are derived by the direct substitution of the fatty acids (see p. 209).

2. *β-Hydroxy Acids.*—The outstanding general difference between the α- and the β-hydroxy-acids is the comparative ease with which the latter lose the elements of water and are converted into unsaturated acids. Thus β-hydroxybutyric acid yields crotonic acid by distillation with 50% aqueous sulphuric acid. β-Hydroxyvaleric acid is converted into a mixture of unsaturated acids either by distillation or by heating in alkaline solution (Fittig and Spencer, *Annalen*, 1894, **283**, 78). These acids show no tendency to yield lactones.

Esters of the β-hydroxy-acids also eliminate the elements of water under suitable conditions. It has been recently studied in detail by Kon and Nargund (*J.*, 1932, 2461), who find that a mixture of αβ- and βγ-unsaturated esters is formed, the relative proportions of the products being dependent on the dehydrating agent used.

3. *γ-Hydroxy-Acids.*—Free γ-hydroxy-acids liberated from their salts are converted more or less readily into the corresponding lactones.

$$R{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$



$$R{\cdot}\underset{\lfloor O}{CH}{\cdot}CH_2{\cdot}CH_2{\cdot}\underset{\rfloor}{CO}$$

Measurements of the rate of formation of lactones in this way from γ-hydroxy-butyric and -valeric acids, and also of the rate of hydrolysis of lactones, indicate that the equilibrium in aqueous solution lies on the side of lactone formation. The equilibrium mixture contains about 90% of the lactone (Johansson and Sebelius, *Ber.*, 1918, **51**, 480; Kailan, *Z. phys. Chem.*, 1919, **94**, 111).

4. *Phenolic Acids.*—In these acids the phenolic hydroxyl can be acylated, alkylated, and in general furnishes colour reactions with ferric chloride.* The carboxyl group also exhibits many of its normal reactions, such as the formation of salts and esters. The reaction towards phosphorous tri- and penta-chlorides, however, is not restricted to the formation of the acid chloride, for interaction between the phosphorus halide and the phenolic hydroxyl occurs with the formation of the phosphoric or phosphorous ester of the acid chloride. By the further action of phosphorus pentachloride, the phenolic hydroxyl may be replaced by chlorine, although the reaction is not a smooth one (Anschütz and G. D. Moore, *Annalen*, 1887, **239**, 343; Anschütz, *Ber.*, 1897, **30**, 223).

If, however, the phenolic hydroxyl group is acetylated, reaction with phosphorus halides proceeds normally with the production of acylated acid chlorides.

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* Some phenolic acids give no coloration with ferric chloride. Some of these exceptions are noted in Table XII.

One of the most important of these acids is salicylic acid. It furnishes a series of dehydration products under the influence of suitable dehydrating agents. Of these salicylsalicylic acid is formed by the action of thionyl chloride or phosphoryl chloride on a benzene solution of the acid in presence of a limited amount of a tertiary amine. Tetrasalicylide and polysalicylide are formed by the action of phosphoryl chloride on a toluene solution of the acid. Under other conditions—namely, distilling with acetic anhydride—notable amounts of xanthone are formed (W. H. Perkin, sen., *J.*, 1883, 43, 35).

(e) *Keto-Acids.*

Owing to the presence of the carbonyl group, these acids can react with phenylhydrazine, hydroxylamine, and semicarbazide. The instability of these acids is dependent on the position of the carbonyl with respect to the carboxyl group. Thus, while the α-keto-acids are comparatively stable, β-keto-acids eliminate carbon dioxide very readily with the formation of ketones. The γ-keto-acids are, in general, more stable than the α-keto-acids.

1. *α-Keto-Acids.*—These acids can undergo degradation to yield either aldehydes or acids (Schemes *a* and *b*).

$$\mathrm{R{\cdot}CO{\cdot}CO_2H} \begin{array}{l} \nearrow \mathrm{R{\cdot}CHO} + \mathrm{CO_2} \qquad . \quad . \quad (a) \\ \searrow \mathrm{R{\cdot}CO{\cdot}OH} + \mathrm{CO} \quad . \quad . \quad . \quad . \quad (b) \end{array}$$

Many α-keto-acids eliminate carbon monoxide on gently warming with concentrated sulphuric acid on the water-bath. When the evolution of gas has ceased, the solution is poured into water, and the resulting acid either filtered off or extracted with ether (Claisen, *Ber.*, 1879, **12**, 631; Beilstein and Wiegand, *ibid.*, 1884, **17**, 841; Bouveault, *Bull. Soc. chim.*, 1897, [ii], **17**, 365, 940; compare Debus, *J.*, 1904, **85**, 1391). It should be noted that some aliphatic α-keto-acids are decomposed largely with the production of the aldehyde by heating them with 10% aqueous sulphuric acid at 150° (Beilstein and Wiegand, *loc. cit.*).

The formation of carboxylic acids is brought about more conveniently by oxidation in aqueous solution with the calculated amount of 30% hydrogen peroxide. By this means pyruvic acid is oxidised to acetic acid, while benzoylformic acid yields benzoic acid (Hollemann, *Proc. K. Akad. Wetensch. Amsterdam*, 1904, **6**, 715).

Preparation of Cinnamylidene Acetic Acid.—10 G. of the sodium salt of cinnamylidenepyruvic acid, $\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO{\cdot}CO_2Na}$, are dissolved in 200 c.c. of water, the solution is cooled in ice, and stirred during the addition of 6 c.c. of perhydrol. The oxidising agent is added over a period of 5—6 minutes. The solution becomes turbid, carbon dioxide is evolved and a precipitate commences to separate. Stirring is continued as long as any gas is evolved. The solution is acidified with 2*N*-sulphuric acid when the oxidation is completed. The precipitated acid is collected by filtration, washed with water, and dried under reduced pressure over calcium chloride—yield 7 g. Crystallisation from benzene furnishes the acid as colourless plates, m. p. 165—166° (Friedmann and Mai, *Helv. Chim. Acta*, 1931, **14**, 1213).

Aryl keto-acids are smoothly converted into aldehydes by Bouveault's method, which consists in heating the acid with an excess of aniline till the evolution of carbon dioxide and water ceases. Vacuum distillation removes the excess of aniline from the azomethine; the aldehyde is obtained by distillation of the azomethine with 25% sulphuric acid (Bouveault, *Bull. Soc. chim.*, 1896, [iii], **15**, 1018; 1897, [iii], **17**, 365).

$$\mathrm{R{\cdot}CO{\cdot}CO_2H} \longrightarrow \mathrm{R{\cdot}C{:}NPh{\cdot}CO_2H} \longrightarrow \mathrm{R{\cdot}CH{:}NPh}$$

Some keto-acids, owing to the tendency to eliminate carbon dioxide, can take the place of aldehydes in the Perkin reaction (Homolka, *Ber.*, 1885, **18**, 987), or in the condensation with dimethylaniline in presence of zinc chloride (Peter, *Ber.*, 1885, **18**, 539).

2. β-*Keto-Acids.*—Free acids of this class are almost entirely derived from the corresponding esters by hydrolysis. Their isolation from this source requires carefully regulated conditions, for the free acids are unstable. The sodium salt of acetoacetic acid has been obtained by keeping the ester in contact with a cold dilute aqueous solution of sodium hydroxide for 24 hours (Ceresole, *Ber.*, 1882, **15**, 1871). Free benzoylacetic acid has been obtained by W. H. Perkin, jun., and Colman (*J.*, 1886, **49**, 157) by hydrolysis of the ester with concentrated sulphuric acid at room temperature. The alkyl-substituted derivatives of this acid are, however, not readily obtained by this treatment. They result, however, by hydrolysis with cold dilute alkali (Hope and W. H. Perkin, jun., *J.*, 1909, **95**, 2045). The free acids thus obtained are unstable, losing carbon dioxide on heating.

Under more vigorous conditions of hydrolysis β-keto-esters undergo fission to yield either ketones or acids. As one or two alkyl groups can be easily introduced into the methylene group adjacent to the carboxyl group, the controlled hydrolysis of esters of β-keto-esters is of considerable importance for the synthesis of ketones and acids.

$$\mathrm{CH_3{\cdot}CO{\cdot}CRR'{\cdot}CO_2Et} \begin{array}{l} \nearrow \mathrm{CH_3{\cdot}CO{\cdot}CHRR' + CO_2 + EtOH} \qquad (a) \\ \searrow \mathrm{CH_3{\cdot}CO_2H + RR'CH{\cdot}CO_2H + EtOH}\ (b) \end{array}$$

This introduction of alkyl groups into acetoacetic ester and similar compounds is effected by treating the sodium salt of the enolic form (see p. 103) with the appropriate alkyl halide. A dialkyl-substituted ester is similarly obtained from the monoalkyl derivative.

In general, fission of β-keto-esters to yield ketones (reaction *a*) succeeds best by heating with dilute alkalis or acids or by the action of water at 200° (Connor and Adkins, *J. Amer. Chem. Soc.*, 1932,

54, 3420). More concentrated alkali favours the formation of acids (reaction *b*). It is evident from the studies of J. Wislicenus on the hydrolysis of these esters that both reactions occur concurrently (*Annalen*, 1877, **186**, 221; 1878, **190**, 257; 1881, **206**, 308). The nature of the substituent alkyl groups has, however, some influence in determining the relative proportions of ketone and acid.

β-Keto-esters undergo fission to yield esters of nitroso fatty acids when subjected to the action of nitrous fumes. The reaction is represented by the following scheme:

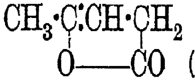
$$R\cdot CO\cdot CH(Alk)\cdot CO_2Et \qquad NO\cdot CH(Alk)\cdot CO_2Et + R\cdot CO_2H.$$

The formation of nitroso-compounds occurs most readily when $R = H$ or methyl (J. Schmidt and co-workers, *Annalen*, 1910, **377**, 23; 1913, **398**, 251).

3. *γ-Keto-Acids.*—In contrast to the β-keto-acids, the γ-keto-acids do not appear to be enolic. They are, moreover, comparatively stable, and generally yield phenylhydrazones, oximes, and semicarbazones. The carbonyl group may be reduced in alkaline solution with the formation of the salts of γ-hydroxy-acids.

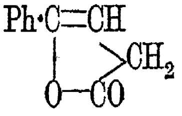
They undergo a characteristic reaction on distillation alone or, better, with acetic anhydride; the lactone of a hydroxy-βγ-unsaturated acid being formed. Thus, lævulic acid (I) yields angelica lactone (II); benzolypropionic acid (III) gives a mixture of (IV) and (V) (Wolff, *Annalen*, 1885, **229**, 249; Thorne, *Ber.*, 1885, **18**, 2263; *J.*, 1881, **39**, 343; Thiele, *Annalen*, 1901, **319**, 144; Fittig, *ibid.*, 1897, **299**, 17).

$CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot CO_2H$
(I.)

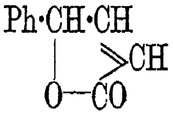


$\begin{array}{l}CH_3\cdot C{:}CH\cdot CH_2\\ \qquad O\text{——}CO\end{array}$
(II.)

$Ph\cdot CO\cdot CH_2\cdot CH_2\cdot CO_2H$
(III.)



(IV.)



(V.)

CHAPTER VI

DERIVATIVES OF THE CARBOXYLIC ACIDS

- (1) Amides.
  - (*a*) Hydrolysis.
  - (*b*) Salt Formation.
  - (*c*) Reaction with Nitrous Acid.
  - (*d*) Reaction with Bromine and Chlorine.
  - (*e*) Reaction with Phosphorus Pentachloride.
  - (*f*) Alkylation of Amides.
- (2) Acyl Chlorides, Bromides, and Fluorides.
  - (*a*) Hydrolysis.
  - (*b*) Conversion into Esters and Amides.
  - (*c*) Replacement of Chlorine by -Br, -I, -F, -CN, $-NO_3$ Groupings.
  - (*d*) Reaction with Diazomethane.
  - (*e*) Reaction with Zinc Alkyl Halides.
  - (*f*) Acid Fluorides.
- (3) Acid Anhydrides.
- (4) Carboxylic Peracids and Peroxides.
- (5) Esters.
  - (*a*) Hydrolysis.
  - (*b*) Alcoholysis.
  - (*c*) Condensation.
  - (*d*) Reaction with Grignard Reagent.
- (6) Reduction of Carboxylic Acids, their Esters, Amides, and Chlorides.
- (7) Nitriles.
  - (*a*) Hydrolysis.
  - (*b*) Alcoholysis.
  - (*c*) Reduction.
  - (*d*) Formation of Imino-Ethers.
  - (*e*) Reaction with Phenols. (Hoesch Synthesis.)
  - (*f*) Conversion to Aldehydes.
  - (*g*) Reaction with Grignard Reagent.
  - (*h*) Other Reactions.

(1) *Amides.*

(a) *Hydrolysis.*—Simple amides of the type $R{\cdot}CO{\cdot}NH_2$ are hydrolysed to the corresponding carboxylic acids by heating under reflux with an excess of aqueous alkali hydroxide or aqueous alcoholic potash till the evolution of ammonia has ceased. Hot aqueous mineral acids act similarly.

$$R{\cdot}CO{\cdot}NH_2 + H_2O \longrightarrow R{\cdot}CO{\cdot}OH + NH_3$$

Although most amides are hydrolysed under these conditions, some are more resistant. Thus 2 : 6-dibromobenzamide is not attacked by heating at 170° with aqueous sulphuric acid of 80% concentration (Sudborough, *J.*, 1895, 67, 602). Many other derivatives of benzamide with substituents in the 2 : 6-positions are also comparatively resistant (Claus, *Annalen*, 1891, **265**, 377; Claus and Beysen, *ibid.*, 1891, **266**, 226; Claus and Beck, *ibid.*, 1893, **269**, 212; Jacobsen, *Ber.*, 1889, **22**, 1220). Among other amides which are difficult to convert into acids by hydrolysis are triphenylacetamide (Heyl and V. Meyer, *Ber.*, 1895, **28**, 2782), dibenzylmethylacetamide, and dimethylbenzylacetamide (Haller and Bauer, *Compt. rend.*, 1909, **149**, 5). The preparation of acids from such amides is very conveniently effected by Bouveault's method described later (p. 251). It is noteworthy that diethylmalonamide is markedly more resistant towards alkali hydrolysis than malonamide (E. Fischer, *Ber.*, 1902, **35**, 852).

The substituted amides of the type R·CO·NR′R″ (R′ and R″ are alkyl) resemble the simple amides in the ease of hydrolysis. The acyl derivatives of the aromatic amines are, however, more resistant. Hydrolysis of these with aqueous alkaline solutions is in general less satisfactory than hydrolysis with hot mineral acids. Thus acetanilide and its homologues are resolved into free carboxylic acid and arylamine salt by heating under reflux with 20% aqueous hydrochloric acid or constant-boiling hydrobromic acid or 50% aqueous sulphuric acid. With these amides also the retarding effect of *ortho*-substituents is observed. Thus 2-acetylamino-*m*-xylene is scarcely attacked by boiling with concentrated hydrochloric acid, and this resistance enables it to be isolated in a pure state from a mixture of acetylated isomeric amines (compare Morgan and Hickinbottom, *J.S.C.I.*, 1926, **45**, 222T; Nölting and Forel, *Ber.*, 1888, **21**, 3150).

(b) *Salt Formation.*—Although the basicity of the NH_2 group in amides is considerably reduced by the presence of an acyl group, yet amides are able to combine with halogen halides to form salts. Thus a solution of acetamide in ether and alcohol which has been saturated with a halogen hydride yields salts of the following type: $(CH_3CO{\cdot}NH_2)_2,HCl$; $(CH_3{\cdot}CO{\cdot}NH_2),HBr$; $(CH_3{\cdot}CO{\cdot}NH_2)_2,HI$. Addition compounds of propionamide and of formamide with halogen hydrides have also been described (A. Werner, *Ber.*, 1903, **36**, 153). The acyl derivatives of arylamines behave similarly. Many of these yield well-characterised and crystalline salts by treatment of the acyl derivative with concentrated acid (compare Dadswell and Kenner, *J.*, 1927, 1104). The acetyl derivative of 3-methylamino-*o*-xylene even yields a platinichloride and an aurichloride (Menton, *Annalen*, 1891, **263**, 320).

Although amides can combine additively with acids, the compounds thus formed are extensively hydrolysed by water, so that in dilute aqueous acids the amides exist free, and not as salts.

The amino-group of amides reacts with alkali metals or sodamide to give metal derivatives, presumably of the general type R·CO·NH·Na or more probably R·C(ONa)⁚NH. Not only are sodium derivatives of formamide, acetamide and propionamide known, but unstable silver salts have been prepared (Titherley, *J.*, 1897, **71**, 467). Mercury salts of acetamide and its homologues have long been known (Strecker, *Annalen*, 1857, **103**, 324). A number of salts of formamide with heavy metals have also been described (Rohler, *Z. Elektrochem.*, 1910, **16**, 429).

The formation of the sodium derivatives of acyl arylamines is utilised for the preparation of pure secondary amines (see 268).

Urea and its alkyl derivatives forms well-defined salts such as nitrate and oxalate which serve for characterisation and for separation from mixtures.

(c) *Reaction with Nitrous Acid.*—Amides containing the grouping $R{\cdot}CO{\cdot}NH_2$ react with nitrous acid to evolve nitrogen and form the corresponding acid :

$$R{\cdot}CO{\cdot}NH_2 + HNO_2 \longrightarrow R{\cdot}CO{\cdot}OH + N_2 + H_2O.$$

This behaviour is a general one, and is analogous to that of the primary aliphatic amines. Its value lies in the fact that it provides an alternative to hydrolysis for the conversion of amides into acids. It can be applied when the hydrolytic methods are unsatisfactory (Bouveault, *Bull. Soc. chim.*, 1892, [iii], **9**, 368). A general description of its application for this purpose is given on p. 251.

Amides of the type $R'NH{\cdot}CO{\cdot}R$ contain an imino-group capable of reacting with nitrous acid to furnish a nitroso-derivative of the general formula $R'N(NO){\cdot}COR$. The best-known nitroso-derivatives of this class are derived from anilides ($R' =$ aryl) and from alkyl ureas ($-COR = CONH_2$) and alkyl urethanes ($-COR = -CO_2Et$).

Nitrosoanilides are prepared by passing nitrous fumes into a well-cooled solution of the anilide in acetic acid. The experimental operations are illustrated by the following descriptions.

Preparation of N-*Nitrosobenzoyl*-o-*toluidine* (I).—A suspension of finely-divided benzoyl-*o*-toluidine is obtained by quickly cooling a mechanically stirred solution of 5 g. of the benzoyl derivative in 30 c.c. of warm acetic acid. The mixture is cooled in ice and then nitrous fumes are passed in till all the suspended material has dissolved. The solution has a dark green colour, and if after keeping for 5 minutes there is no change in colour, the solution is poured on ice. The nitroso-derivative separates as an oil, which soon becomes crystalline. It is collected by filtration, washed with ice-water, and dried on porous earthenware. It is purified by cautious precipitation from acetone solution by the addition of ice-water. It is then obtained as a yellowish crystalline compound with a saffron-like odour, m. p. 62—63° (Jacobson and Huber, *Ber.*, 1908, **41**, 663).

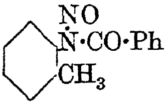
Nitroso-derivatives from acetanilide, acetnaphthalide, and *p*-bromoacetanilide are similarly prepared (O. Fischer, *Ber.*, 1876, **9**, 463; Hantzsch and Wechsler, *Annalen*, 1902, **325**, 237).

Preparation of N-*Nitrosomethylurethane* (II).—Nitrous fumes are passed into methylurethane, covered with an equal volume of ether, till the colour of the solution is dirty grey. It is then washed with water, with sodium carbonate solution, and then dried in contact with anhydrous sodium sulphate. The product may be purified by distillation under reduced pressure, but this is unnecessary if it is to be used for the preparation of diazomethane. Nitrosomethylurethane is a yellowish-red liquid, b. p. 70°/27 mm. (v. Pechmann, *Ber.*, 1895, **28**, 856).

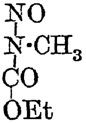
This compound is also obtained, although less conveniently, by the action of aqueous nitrous acid. This method can, however, be successfully used for the preparation of nitroso-alkyl ureas.

Preparation of Nitrosomethyl Urea (III).—A solution of methyl urea (44·4 g.) and sodium nitrite (43·2 g.) in 400 c.c. of water in a wide-necked bottle is cooled in ice-water. While the solution is stirred mechanically, diluted sulphuric acid (30 g. concentrated sulphuric acid in 150 c.c. of water) is added gradually. There is an evolution of gas and the nitroso-compound separates. After 2 hours, the precipitate is collected, washed with water, and dried in a vacuum desiccator—yield 49 g.—pale yellow crystals, m. p. 121° (E. A. Werner, *J.*, 1919, **115**, 1096).

The nitroso-derivatives from ethyl, *n*-butyl, and *iso*amyl ureas are similarly prepared (compare v. Brüning, *Ber.*, 1888, **21**, 1809).

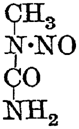


(I.)



$$\begin{array}{c}\mathrm{NO}\\ |\\ \mathrm{N{\cdot}CH_3}\\ |\\ \mathrm{CO}\\ |\\ \mathrm{OEt}\end{array}$$

(II.)



$$\begin{array}{c}\mathrm{CH_3}\\ |\\ \mathrm{N{\cdot}NO}\\ |\\ \mathrm{CO}\\ |\\ \mathrm{NH_2}\end{array}$$

(III.)

(d) *Reaction with Bromine and Chlorine.*—Acid amides of the type $R{\cdot}CO{\cdot}NH_2$ or $R{\cdot}CO{\cdot}NHR'$ react with hypochlorous or hypobromous acids to yield chlor- or brom-amides, the halogen replacing the hydrogens of the amino-group. This reaction is also shared by sulphonamides (Chattaway, *J.*, 1905, **87**, 145). The preparation of these substances is illustrated by the following examples.

Preparation of Acetochloramide.—A solution of acetamide (59 g.) in 100 c.c. of water is mixed with 40 g. of zinc oxide and then cooled to — 5° by an external bath of ice and salt. A rapid stream of chlorine is passed into the cooled solution till it has increased in weight by 71 g.

Acetochloramide crystallises out, and it is collected after cooling the product to — 15°.

The chloramide is purified by crystallisation from boiling light petroleum, m. p. 110°—yield may reach 60—70 g. (Mauguin, *Ann. Chim. Phys.*, 1911, [viii], **22**, 305).

Preparation of Acetobromamide.—A solution of 56 g. of potassium hydroxide in 100 c.c. of water is added to a mixture of 59 g. of acetamide and 160 g. of bromine, which is cooled by an external bath of ice and salt.

A precipitate of potassium bromide separates, leaving a pale yellow solution of bromacetamide, which sets to a thick paste of crystals on nucleation with a fragment of crystalline bromacetamide. After collecting the crystalline bromacetamide by filtration, a further amount can be obtained by chilling the filtrate to — 15°. It is purified by crystallisation from 10 times its weight of boiling chloroform, and is obtained as a mixture of hydrated and anhydrous forms (Mauguin, *loc. cit.*, p. 302).

A variation of this procedure consists in dissolving the amide and the bromine in chloroform before adding the alkali. It has been applied successfully to the preparation of *iso*butyrobromamide, and of some α-alkylvalerobromamides (Pyman, *J.*, 1913, **103**, 857).

Preparation of Benzobromamide.—Benzamide (12 g.) is added to a solution of 16 g. of bromine in 160 g. of chloroform, dissolution of the amide being achieved by raising the mixture to boiling. It is then cooled to 40° and a solution of 5·6 g. of potassium hydroxide in 30 c.c. of water added while the mixture is stirred.

Benzobromamide separates out on cooling, and is purified by crystallisation from chloroform—yield 15 g. (Mauguin, *loc. cit.*, p. 310).

Preparation of Phenylacetobromamide.—1 Mol. proportion of bromine dissolved in a solution of 4 mol. proportions of potassium hydroxide in 16 parts of water is added to 1 mol. proportion of phenylacetamide. On neutralising the solution with acetic acid, the bromamide separates out. It crystallises from benzene in needles, m. p. 123—125°.

Preparation of Acetochloranilide.—Acetanilide is suspended in potassium bicarbonate solution and the necessary amount of bleaching-powder added. The chloramide is extracted with chloroform. It is purified by crystallisation from a mixture of chloroform and light petroleum (b. p. 80—100°) (Chattaway and Orton, *J.*, 1899, **75**, 1050; 1901, **79**, 279).

Preparation of Arylsulphondichloramides.—The following general method is due to Chattaway (*J.*, 1905, **87**, 148).

The sulphonamide is added to an excess of saturated bleaching-powder solution, and when the amide has dissolved, the solution is cooled in ice. Acetic acid is then slowly added. The dichloramide which separates is taken up in chloroform and the solution thus obtained is shaken with freshly acidified bleaching-powder solution to ensure the absence of any unchanged sulphonamide. The chloroform solution is dried over fused calcium chloride, and then evaporated under reduced pressure. The dichloramides thus obtained generally crystallise well from a mixture of light petroleum and chloroform.

The brom- and chlor-amides readily part with halogen, and consequently can be used for halogenation. An interesting example of this tendency is found in the behaviour of phenylacylchloramines, which are converted into chlorophenylacylamines under the influence of acids (Chattaway and Orton, *J.*, 1899, **75**, 1046; 1900, **77**, 789; 797, 800; 1901, **79**, 274).

$$C_6H_5{\cdot}NCl{\cdot}CO{\cdot}CH_5 \longrightarrow ClC_6H_4{\cdot}NH{\cdot}CO{\cdot}CH_3$$

All the chlor- and brom-amides liberate iodine from acidified potassium iodide solution.

Halogen amides of the general type R·CO·NHHal yield salts (Mauguin, *loc. cit.*, p. 311; compare Hantzsch and Dollfus, *Ber.*, 1902, **35**, 249; Hoogewerff and van Dorp, *Rec. trav. chim.*, 1888, **6**, 373; 1896, **15**, 107). The interest attached to these salts lies in their decomposition. In presence of an excess of alkali, they form primary amines.

$$R{\cdot}CO{\cdot}NHBr + 3KOH \longrightarrow RNH_2 + KBr + K_2CO_3 + H_2O$$

Hofmann employed this type of reaction (*Ber.*, 1882, **15**, 752; 1884, **17**, 1406) for the preparation of aliphatic amines. It succeeds well as far as amylamine; the yields of the higher amines are seriously reduced by the occurrence of side reactions—the formation of a nitrile being the most serious. The method cannot therefore be used in this form for the preparation of aliphatic primary amines higher than amylamine.

The application of the reaction to amides of dibasic acids does not appear to have been examined very extensively (compare Weidel and Roithner, *Monatsh.*, 1896, **17**, 172; van Dam, *Rec. trav. chim.*, 1897, **16**, 26), although one recorded application is for the preparation of tetramethylenediamine from the diamide of adipic acid

(F. Baeyer & Co., D.R.-P. 232,072). Primary aromatic amines have been prepared from the corresponding amides by its use, and it is the basis of the technical method for the preparation of anthranilic acid.

The formation of primary amines from bromamides is presumably due to the initial decomposition of their salts into *iso*cyanic esters which subsequently undergo hydrolysis by the excess of aqueous alkali.

$$R\cdot CO\cdot NNaBr \longrightarrow R\cdot CO\cdot N< + NaBr \longrightarrow R\cdot N{:}C{:}O \xrightarrow{H_2O} R\cdot NH_2 + CO_2$$

Mauguin (*loc. cit.*, p. 316) has satisfactorily demonstrated the formation of isocyanic esters by the decomposition of the pure alkali salts of bromamides.

The intermediate formation of *iso*cyanate in the Hofmann degradation of amides can be made to account also for the formation of acyl alkyl ureas which are obtained by the decomposition of the bromamide in presence of unchanged amide (Hofmann, *Ber.*, 1881, **14**, 2725; 1882, **15**, 752); for the formation of urethanes if the bromamide is treated with alcoholic alkoxide solutions, and for the production of symmetrical ureas which is observed under suitable conditions. The reactions involved in the formation of these substances from *iso*cyanates are summarised by the following equations:

$$\begin{array}{lll} R\cdot N{:}C{:}O + NH_2\cdot CO\cdot R & \longrightarrow & R\cdot CO\cdot NH\cdot CO\cdot NHR \\ R\cdot N{:}C{:}O + OH\cdot R' & \longrightarrow & R\cdot NH\cdot CO\cdot OR' \\ 2R\cdot N{:}C{:}O + H_2O & \longrightarrow & R\cdot NH\cdot CO\cdot NHR + CO_2 \end{array}$$

These apparently simple explanations are not altogether satisfactory, for it has been found that the *iso*cyanic ester is not sufficiently reactive to account for the products formed (Jeffreys, *Amer. Chem. J.*, 1899, **22**, 14; Pyman, *loc. cit.*; compare Stieglitz and Earle, *Amer. Chem. J.*, 1903, **30**, 412). The following papers should also be consulted: Mohr, *J. pr. Chem.*, 1909, [ii], **79**, 281; **80**, 1; Odenwald, *Annalen*, 1919, **418**, 316.

Preparation of n-*Heptylamine.*—Bromine (1 mol. proportion) is dissolved in a solution of 4 mol. proportions of potassium hydroxide in 16 parts of water. The resulting solution is added to 1 mol. proportion of the amide of caprylic acid. The solution is heated rapidly and then steam distilled. Heptylamine, b. p. 155°, is obtained—yield 60—65% of theory (Hoogewerff and van Dorp, *Rec. trav. chim.*, 1888, **6**, 373).

Preparation of Anthranilic Acid.—A solution of sodium hydroxide (20 g.) in 100 c.c. of water is stirred mechanically and cooled in a freezing mixture. After gradually adding 16 g. of bromine, a paste of phthalimide is introduced gradually and the reaction mixture taken from the freezing mixture. When it has become clear, 12 g. of powdered caustic soda are stirred in. The temperature is now gradually raised to 80° and subsequently cooled. It is then neutralised with approximately 50 c.c. of concentrated hydrochloric acid, and the anthranilic acid is precipitated by the addition of 15 c.c. of glacial acetic acid.

After keeping overnight, the anthranilic acid is collected and washed with a small amount of water. It is purified by crystallisation from warm water or from light petroleum (Hoogewerff and van Dorp, *Rec. trav. chim.*, 1891, **10**, 4; compare T. S. Moore, Marrack, and Proud, *J.*, 1921, **119**, 1786).

Preparation of Pentadecylcarbamic Ester.—A solution of 4·6 g. of sodium in 115 g. of methyl alcohol is added to 25·5 g. of palmitamide in 65 g. of methyl alcohol, and to the resulting solution, bromine (16 g.) is added drop by drop. The reaction is completed by warming on a water-bath for 10 minutes. It is then neutralised by the addition of acetic acid and the alcohol distilled off. The residue is freed from sodium salts by washing with water, and from unchanged palmitamide by dissolving once or twice in warm light petroleum (b. p. 70—80°) (Jeffreys, *Ber.*, 1897, **30**, 898; *Amer. Chem J.*, 1899, **22**, 14; compare Gutt, *Ber.*, 1907, **40**, 2062).

Preparation of m-*Bromaniline.*—A solution of 10·2 g. of caustic potash and 10·8 g. of bromine in 100 c.c. of water is poured on 12 g. of *m*-brombenzamide and the mixture added to 14·4 g. of potash in 25 c.c. of water. The temperature is maintained at 70—75° for about ¾ hour, and the amine is then driven over in steam. The yield of crude product is 8·9 g. (Beckmann and Correns, *Ber.*, 1922, **55**, 850).

Preparation of Methylacetyl Urea.—An approximately 20% solution of potassium hydroxide containing 56 g. of alkali is added to 59 g. of acetamide dissolved in 88 g. of bromine. The mixture, which loses its red colour almost immediately, is heated in a boiling water-bath. After a few minutes there is an effervescence, and the solution becomes yellow. It is important that the solution should be kept slightly acid or just neutral at this stage. It must on no account be allowed to become alkaline. The solution is then warmed for a short time and allowed to cool. The crystallisation of methylacetyl urea is complete after keeping for 24 hours. A further amount may be obtained by evaporating the filtrate from the first crop of crystals at room temperature —yield 37—44 g. (Odenwald, *Annalen*, 1918, **416**, 228).

Preparation of iso*Butyl*iso*valeryl Urea.*—*iso*Valeramide (5·5 g.) is dissolved as far as possible in 1·4 c.c. of bromine. 28 C.c. of a 10% solution of caustic potash are then added slowly and with stirring. The mixture is afterwards heated for 15 minutes on a water-bath.

In a short time an oil separates on the surface. It solidifies on cooling and is purified by several crystallisations from alcohol, when pure *iso*butyl*iso*valeryl urea, m. p. 100—104°, is obtained—yield 2·3 g.

Unchanged *iso*valeramide is obtained from the mother-liquor by evaporation and subsequent extraction of the residue by alcohol (Odenwald, *Annalen*, 1919, **418**, 327).

(e) *Reaction with Phosphorus Pentachloride.*—When equimolecular proportions of acetanilide and phosphorus pentachloride are mixed, hydrogen chloride is evolved and the product is a mixture of phosphorus oxychloride and an imino-chloride (V).

$$\mathrm{Ph{\cdot}NH{\cdot}CO{\cdot}CH_3 + PCl_5} \qquad \underset{\text{(IV.)}}{\mathrm{Ph{\cdot}NH{\cdot}CCl_2{\cdot}CH_3}} \qquad \underset{\text{(V.)}}{\mathrm{Ph{\cdot}N{:}CCl{\cdot}CH_3}}$$

This reaction appears to be a fairly general one for anilides, and presumably occurs with the intermediate formation of (IV). With such amides as acetamide and benzamide, a similar type of reaction no doubt occurs, but the final product does not appear to be simple (Wallach, *Annalen*, 1877, **184**, 5).

Preparation of Cinnamphenyliminochloride, Ph·CH:CH·CCl:NPh.—Finely-powdered cinnamanilide (10 g.) which has been dried over phosphorus pentoxide is suspended in 150 c.c. of dry toluene. Powdered phosphorus pentachloride (10 g.) is rapidly added, the mixture shaken, and then heated on a water-bath. The suspended material dissolves and hydrogen chloride is evolved. When the reaction is complete, the solvent and phosphorus oxychloride are removed by distillation at 50—60° under reduced pressure. The imino-chloride remains as a transparent reddish mass (Sonn and Müller, *Ber.*, 1919, **52**, 1930).

Preparation of p-*Carbethoxybenzophenyliminochloride*,
$EtOCO\cdot OC_6H_4\cdot CCl{:}NPh$
—Powdered dry *p*-carbethoxybenzanilide (15 g.) is suspended in 30 c.c. of dry toluene. After adding 11 g. of phosphorus pentachloride and thoroughly shaking the mixture, it is heated on a water-bath. A clear, almost colourless solution results after about ½ hour, when the solvent and phosphorus oxychloride are removed by distillation under reduced pressure.

The residue of iminochloride is purified by solution in five times its weight of hot petroleum ether (b. p. 30—100°). On cooling, it separates from this solution as colourless acicular crystals, m. p. 84° (Sonn and Müller, *loc. cit.* p. 1931).

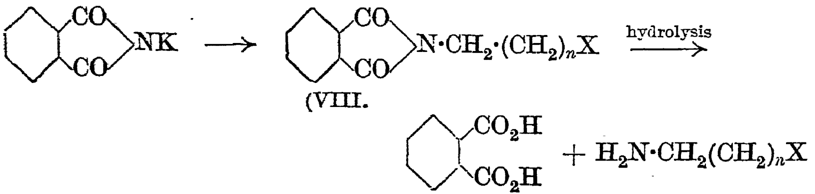
(f) *Alkylation of Amides.*—When the alkali metal derivatives of the anilides are treated with alkyl halides, the alkali metal is replaced by alkyl with the formation of the acyl derivative of an alkylaniline. A description of this process of alkylation is given on p. 268. When the alkali metal derivatives are replaced by silver derivatives, the product of alkylation may contain other products. Thus the silver salt of formanilide furnishes a mixture of the formyl derivative of an alkylaniline (VI) and a formophenylimino-ether (VII) when it is treated with methyl or ethyl iodides.

$$C_6H_5NH\cdot COH \begin{array}{l} \xrightarrow{\text{alk I}} C_6H_5N(Alk)\cdot COH \quad (\text{VI.}) \\ \xrightarrow[\text{alk I}]{} C_6H_5\cdot N{:}CH(OAlk) \quad (\text{VII.}) \end{array}$$

Other amides such as acetanilide, benzanilide, and many nuclear-substituted benzamides behave similarly (Wheeler and Johnson, *Amer. Chem. J.*, 1899, 21, 185; 1900, 23, 136; Lander, *J.*, 1903, 83, 415; Lander and Jewson, *ibid.*, p. 766).

It appears that the relative proportions of the *O*-ether and the *N*-alkyl derivative depend partly on the amide employed, and on the experimental conditions such as temperature and duration of the reaction. The alkyl halide also has an important effect, methyl iodide generally being more effective in bringing about the formation of the *N*-alkyl derivative. This reaction is further complicated by the tendency of the imino-ether to rearrange to the isomeric amide under the conditions of the reaction.

An important application of the alkylation of amides is Gabriel's method for the preparation of primary amines. It consists in allowing potassium phthalimide to react with a suitable halogen compound. The product is a *N*-substituted phthalimide (VIII) which yields a primary amine (IX) on hydrolysis.



(VIII.

(IX.)

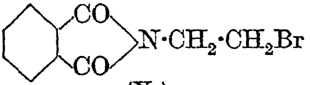
A large variety of halogen compounds have been successfully employed in this reaction, such as alkyl iodides and bromides, benzyl chloride and some of its nuclear-substituted derivatives, allyl bromide, ethylene dibromide, trimethylene and pentamethylene dihalides, some chloroalkyl cyanides such as γ-chlorobutyronitrile, chloro- and bromo-ketones, chlorhydrins and their esters, α-halogen-substituted fatty acids (Gabriel and co-workers, *Ber.*, 1887, **20**, 2224; 888, **21**, 566, 2669; 1887, **20**, 2869; 1889, **23**, 1771; 1892, **25**, 956; 1893, **26**, 2197; 1902, **35**, 3805; Seitz, *ibid.*, 1891, **24**, 2624; ohmann, *ibid.*, p. 2631; A. Neumann, *ibid.*, 1890, **23**, 994). The following descriptions illustrate the method.

Preparation of N-β-bromoethylphthalimide (X).—Potassium phthalimide (150 g.) and ethylene dibromide (180 g.) are heated together under reflux in an oil-bath at 150°. When no more dibromide refluxes, the contents of the flask are thoroughly mixed and again heated till they are a brownish-yellow syrup. About 400—500 c.c. of hot alcohol are now added and the mixture is heated under reflux till the insoluble residue is a yellowish powder free from lumps. The residue consists of (XI) and potassium bromide. The solution is filtered while still hot and the filtrate is distilled to remove the solvent. Crude bromoethyl phthalimide remains as an oil which solidifies to a crystalline cake. It is purified by extraction with 200 c.c. of boiling carbon disulphide. The pure compound separates from the filtrate on cooling as needles, m. p. 82—83°—yield 90 g.

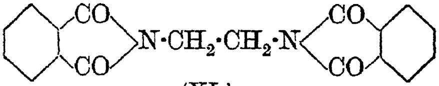
Hydrolysis of N-β-Bromoethylphthalimide to β-Bromoethylamine Hydrobromide.—Bromoethyl phthalimide (20 g.) is heated in sealed tubes at 180—200° for 2 hours with 50—60 c.c. of hydrobromic acid (*d*, 1·49). The product is diluted with water, and the suspended phthalic acid collected by filtration. Evaporation of the filtrate yields a crystalline mass of the hydrobromide of β-bromoethylamine (yield about 15 g.). After crystallisation from 15—20 c.c. of hot ethyl alcohol it is obtained as needle-like crystals.

Preparation of n-*Propylphthalimide* (XII).—Potassium phthalimide is heated in a sealed tube with 1½ times its weight of *n*-propyl bromide for 5 hours at 150—160°. The product is a transparent syrup, which is steam distilled to remove the excess of bromide. The residue solidifies to a crystalline mass which separates from hot alcohol as thick colourless plates, m. p. 66°, b. p. 282°/756 mm.

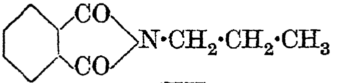
Preparation of Acetonylphthalimide (XIII).—Potassium phthalimide (100 g.), chloracetone (100 c.c.), and dry xylene (100 c.c.) are heated together under reflux at 120—130° with occasional stirring. After about 1 hour the mixture is steam-distilled to remove xylene and chloracetone. A brownish oil remains, which solidifies. It is purified by crystallisation from a large volume of hot water, m. p. 124°—yield 73 g.



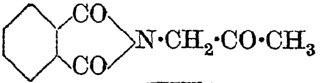
(X.)



(XI.)



(XII.)



(XIII.)

The hydrolysis of the substituted phthalimides is generally accomplished by heating with 20% hydrochloric acid or concentrated hydrobromic acid under reflux or in sealed tubes at 180—190°.

Potassium phthalimide required for these preparations is best prepared by the following method.

A solution of 7·6 g. of potassium hydroxide in 30 c.c. of 75% alcohol is added to a hot solution of 20 g. of phthalimide in 40 c.c. of absolute alcohol. The solution is cooled rapidly, and the precipitate of potassium phthalimide collected by filtration. The filtrate is used for the preparation of a further quantity of potassium phthalimide, by dissolving in it 20 g. of phthalimide and then adding 7·6 g. of potassium hydroxide in 30 c.c. of 75% alcohol. The potassium phthalimide thus prepared is washed with acetone (Hale and Britton, *J. Amer. Chem. Soc.*, 1919, **41**, 843).

(2) *Acyl Chlorides, Bromides, and Fluorides.*

(a) *Hydrolysis.*

The conversion of the acyl chlorides into the corresponding acids by treatment with water is a reaction of general application.

$$R{\cdot}CO{\cdot}Cl + H_2O \qquad R{\cdot}CO{\cdot}OH + HCl$$

Chlorides of aliphatic acids suffer this decomposition by contact with cold water and the reaction may be a violent one. The chlorides of the aromatic acids are more resistant towards hydrolysis; they are in general only slowly hydrolysed by cold water, more rapidly by hot. The most convenient method of converting them into acids is to heat with aqueous alkali under reflux till hydrolysis is complete, and then acidify.

Examples of the retarding effect of negative substituents, such as $-NO_2$ or $-Br$, in the *ortho* position of aromatic acid chlorides, on the rate of hydrolysis have been recorded. Thus 2 : 4 : 6-tribromobenzoyl chloride is volatile in steam, and after boiling with water for 30 minutes is hydrolysed only to the extent of 28%. It is only slowly hydrolysed by boiling aqueous alkali. Similar examples of the comparative stability of similarly constituted chlorides are given by Sudborough (*J.*, 1894, **65**, 1030; 1895, **67**, 587; V. Meyer, 1894, **27**, 3153).

(b) *Conversion into Esters and Amides.*

These reactions are discussed on pp. 79, 80 and 262, 263.

(c) *Replacement of Chlorine* by Br, –I, –F, –CN, $-NO_3$ *Groupings.*

The conversion of acid chlorides into bromides and iodides can be effected conveniently by Staudinger and Anthes' method (*Ber.*, 1913, **46**, 1417), whereby the acyl chloride is saturated with about three times the necessary amount of dry hydrogen bromide or iodide. Subsequent distillation yields the corresponding acyl bromide or iodide.

The preparation of acyl iodides from the corresponding chlorides has been effected by reaction with calcium iodide.

The replacement of the chlorine by fluorine may be achieved by heating with silver fluoride, but the yields are not very satisfactory (Gernez, *Bull. Soc. chim.*, [iii], **5**, 887; Meslans, *Ann. Chim. Phys.*, 1894, [vii], **1**, 405). A more satisfactory process, at least as far as acetyl chloride is concerned, is by the reaction of acetyl chloride with arsenic or antimony trifluorides or zinc fluoride (Meslans, *loc. cit.*); benzoyl chloride yields benzoyl fluoride by reaction with zinc fluoride or potassium acid fluoride (Meslans and Girardet, *Bull. Soc. chim.*, 1896, [iii], **15**, 878; Borodin, *Compt. rend.*, 1863, **55**, 555). For other methods of preparation see p. 230.

The conversion of acyl chlorides into acyl cyanides has been effected by heating the chloride in sealed tubes with silver cyanide, followed by fractionation of the product. The yields obtained are generally not very satisfactory (Hübner, *Annalen*, 1861, **120**, 334; Claisen and Shadwell, *Ber.*, 1878, **11**, 1565; Claisen and Moritz, *ibid.*, 1880, **13**, 2121; Moritz, *J.*, 1881, **39**, 13). A more convenient process consists in the interaction of the acyl chloride with anhydrous hydrogen cyanide and pyridine (Claisen, *Ber.*, 1898, **31**, 1023).

Preparation of p-*Methoxybenzoyl Cyanide.*—Anisoyl chloride (20 g.) and anhydrous hydrogen cyanide (20 g.) are mixed in 200 c.c. dry ether. Anhydrous pyridine (20 c.c.) is gradually added, and the solution kept overnight. The resulting cyanide is washed with water, drained on a tile, and then crystallised several times from light petroleum to remove anisic acid (the acid is the more sparingly soluble). It is finally distilled under high vacuum and the distillate crystallised from a mixture of benzene and light petroleum, m. p. 63—64°—yield 7 g. (Mauthner, *Ber.*, 1909, **42**, 188).

Benzoyl chloride can be converted into benzoyl nitrate by reaction with silver nitrate.

Preparation of Benzoyl Nitrate.—Benzoyl chloride (35 g.) is mixed with finely-powdered silver nitrate (the amount being about 20% in excess of that required by theory) in a flask provided with a phosphorus pentoxide drying tube. The flask is kept at − 15° and shaken continuously for $2\frac{1}{2}$ hours.

At the end of this period the contents of the flask are filtered through a layer of carefully dried asbestos. Approximately pure benzoyl nitrate is obtained as a clear yellow oil which is preferably used directly for nitration (see p. 39).

For the success of this preparation each of the reagents should be dry (Francis, *J.*, 1906, **89**, 1; *Ber.*, 1906, **39**, 3798).

(d) *Reaction of Acid Chlorides with Diazomethane.*—Diazomethane reacts with acyl chlorides in ethereal solution to furnish diazoketones

$$R\cdot CO\cdot Cl + CH_2N_2 \qquad R\cdot CO\cdot CHN_2 + HCl$$

This reaction has been applied to acetyl and chloroacetyl chlorides and to the chlorides of many aromatic acids (Arndt and Amende, *Ber.*, 1928, **61**, 1122; Bradley and Robinson, *J.*, 1928, 1310; Bradley and Schwarzenbach, *ibid.*, p. 2904; Bradley, Robinson, and Schwarzenbach, *ibid.*, 1930, 797).

The yield of diazo-ketone appears to be reduced by the action of the hydrogen chloride which is liberated in the reaction (compare Clibbens and Nierenstein, *J.*, 1915, **107**, 1491). The most suitable conditions for its preparation appear to be to allow 2 mol. props. of diazomethane to react with the acid chloride. Under these conditions, the hydrogen chloride attacks the excess of diazomethane preferentially.

Preparation of ω-Diazoacetophenone.—A solution of 2·8 g. of *p*-nitrobenzoyl chloride in 20 c.c. of ether is added, over a period of 4—5 minutes, to an ethereal solution of diazomethane prepared from 6·3 g. of nitrosomethylurethane.

There is a vigorous evolution of nitrogen accompanied by the separation of crystalline diazo-ketone. The product is kept for 12 hours, then filtered off. A further amount of less pure product is obtained by evaporating the filtrate in a current of air. The product can be purified by crystallisation from ethyl alcohol, m. p. 116—117° (Bradley and Schwarzenbach, *loc. cit.*).

(e) *Reaction of Acid Chlorides with Zinc Alkyl Halides.*—In the action of the zinc alkyl halides on acid chlorides, the reaction is generally restricted to the replacement of the halogen of the acyl chloride by the alkyl group of the zinc alkyl halide. This furnishes a method for the preparation of ketones from acyl chlorides.

$$R{\cdot}CO{\cdot}Cl + Zn(Alk)Hal \qquad R{\cdot}CO{\cdot}Alk + ZnClHal$$

The interaction is brought about by mixing the acid chloride with the zinc alkyl halide dissolved in a suitable indifferent solvent (see p. 375). Although the majority of acyl chlorides react normally to furnish ketones, some αβ-unsaturated acid chlorides yield esters of *tert.*-alcohols as the product of condensation with zinc alkyl halides (Blaise, *Bull. Soc. chim.*, 1911, [iv], **9**, i). γ-Halogen acid chlorides react at 0° to give a mixture of ester of tertiary alcohol and ketone, but at − 20° to −15° the yields of ketones are good (Wohlgemuth, *Compt. rend.*, 1914, **159**, 80). α-Alkoxyacyl chlorides behave abnormally, furnishing ethers as well as ketones (Blaise and Picard, *Ann. Chim. phys.*, 1912, [viii], **25**, 253). The reaction of acyl chlorides with Grignard reagent is referred to on p. 244.

(d) *Acid Fluorides.*—The preparation of acyl fluorides from acyl chlorides by treatment with metal fluorides has already been mentioned on p. 229. A method which is apparently capable of considerable application consists in the action of fluorosulphonic acid on the free acid or on its salts or distillation of a salt of the acid with a salt of fluorosulphonic acid (Traube and Krahmer, *Ber.*, 1919, **52**, 1296)

$$R{\cdot}CO_2X + XFSO_3 \longrightarrow RCOF + X_2SO_4 \quad (X = H \text{ or Metal})$$

Acyl fluorides have also been prepared by the action of hydrogen fluoride on the acid anhydride.

(3) *Acid Anhydrides.*

Compared with the acid chlorides, the anhydrides are comparatively stable to water. Thus acetic anhydride forms a separate layer when it is added to water and is hydrolysed with measurable velocity at room temperature to yield acetic acid (Rivett and Sidgwick, *J.*, 1910, **97**, 1677; Boeseken and Verkade, *Proc. K. Akad.*

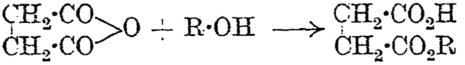
Wetensch. Amsterdam, 1914, **16**, 718). The homologues of acetic anhydride behave similarly. Hydrolysis occurs more rapidly with warm water or by heating with aqueous alkali.

Alcohols yield esters; ammonia and amines yield amides. The reactions are represented by the following equations :

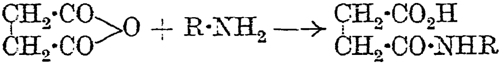
$$(R\cdot CO)_2O + HO\cdot R' \longrightarrow R\cdot CO\cdot OR' + R\cdot CO\cdot OH$$
$$(R\cdot CO)_2O + NH_2R' \longrightarrow R\cdot CO\cdot NHR' + R\cdot CO\cdot OH$$

The applications of these reactions are discussed on pp. 78, 264, 265.

A similar type of reaction occurs with the cyclic anhydrides of dibasic acids, such as succinic and phthalic acids. An amido-acid (II) or an acid ester (I) results as the primary product.



$$\begin{array}{l}CH_2\cdot CO\\ CH_2\cdot CO\end{array}\!\!>O + R\cdot OH \longrightarrow \begin{array}{l}CH_2\cdot CO_2H\\ CH_2\cdot CO_2R\end{array} \qquad (I.)$$



$$\begin{array}{l}CH_2\cdot CO\\ CH_2\cdot CO\end{array}\!\!>O + R\cdot NH_2 \longrightarrow \begin{array}{l}CH_2\cdot CO_2H\\ CH_2\cdot CO\cdot NHR\end{array} \qquad (II.)$$

The formation of compounds of type II is frequently employed for the characterisation of these anhydrides, the products derived by reaction with arylamines being usually crystalline. They are, moreover, converted into anils by heating at temperatures above the melting point (Anschütz, *Ber.*, 1887, **20**, 3214; 1888, **21**, 88; *Annalen*, 1890, **259**, 137 ; Auwers, *ibid.*, 1895, **285**, 227).

(4) *Carboxylic Peracids and Peroxides.*

The comparatively stable and inert peroxides of the aromatic acids result by the interaction of the corresponding acyl chlorides with alkali peroxides or with hydrogen peroxide in presence of alkali.

$$2\ Ph\cdot CO\cdot Cl + Na_2O_2 \longrightarrow (Ph\cdot CO)_2O_2 + NaCl$$

Preparation of Benzoyl Peroxide.—A solution of 15—18 c.c. of 15% aqueous sodium hydroxide and 7·5 g. of benzoyl chloride are added alternately—a few drops at a time—to 25 c.c. of 10% hydrogen peroxide solution cooled by an external bath of ice. The mixture is shaken continuously and should be kept faintly alkaline. When all the reagents have been added, the benzoyl peroxide has separated as a crystalline flocculent solid free from benzoyl chloride. It is collected by filtration under suction, washed with water, and dried on a porous plate.

It may be purified by rapid crystallisation from a small amount of hot alcohol, or by precipitation from concentrated chloroform solution by the addition of methyl alcohol (v. Pechmann and Vanino, *Ber.*, 1894, **27**, 1510).

Benzoyl peroxide has been prepared in good yield by the action of benzoyl chloride on sodium peroxide in water (Gambarjan, *Ber.*, 1909, **42**, 4008). Other peroxides, such as *o*-toluyl, fumaryl, and succinyl peroxides, have similarly been obtained (Vanino and Thiele, *Ber.*, 1896, **29**, 1726).

Benzoyl peroxide is comparatively inert, having no action on permanganate, potassium iodide, or indigo solution. Treatment with alcoholic sodium ethoxide, however, converts it into the sodium salt of perbenzoic acid (Baeyer and Villiger, *Ber.*, 1900, **33**, 1576).

$$(Ph{\cdot}CO)_2O_2 + NaOEt \longrightarrow Ph{\cdot}CO{\cdot}O{\cdot}ONa + EtO{\cdot}OC{\cdot}Ph$$

Preparation of Perbenzoic Acid.—Finely-powdered benzoyl peroxide (121 g.) is suspended in 1·5 l. of dry toluene in a 5-l. round-bottomed flask cooled in a freezing mixture to below − 5°. An ice-cold solution of sodium ethoxide—prepared by dissolving 23 g. of sodium in 500 c.c. of absolute alcohol—is added, and the mixture stirred vigorously. When all the ethoxide has been poured in, 2 l. of ice-water are added, the stirring being continued till practically all the benzoyl peroxide has disappeared. The toluene layer is then separated in a cooled separating funnel, and the aqueous solution extracted with ether to remove the last traces of ethyl benzoate.

The sodium salt of perbenzoic acid is present in the aqueous solution, which is cooled to 0° and acidified by the cautious addition of an ice-cold solution of 54 g. of concentrated sulphuric acid in 50 c.c. of water. During the acidification the solution should be efficiently stirred and the temperature kept as near as possible to 0°. Perbenzoic acid separates as a thick oil which is removed by three extractions with chloroform, 250 c.c. being used for each extraction. The chloroform solution is dried over anhydrous sodium sulphate and kept in an ice-chest till required.

The concentration of the peracid can be determined as follows.

A known volume of the chloroform solution (0·5 c.c. is a convenient amount) is acidified by the addition of several drops of dilute hydrochloric acid, and an excess of potassium iodide solution added. The liberated iodine is titrated with standard thiosulphate solution (1 c.c. of 0·1*N*-thiosulphate = 0·008 g. of active oxygen = 0·0069 g. of perbenzoic acid) (Tiffeneau, *Organic Syntheses*, 1928, **8**, 30).

In contrast to the peroxide, perbenzoic acid is comparatively active, and liberates iodine from acidified potassium iodide. The concentration of the acid in its solution can be determined conveniently by this means.

Perbenzoic acid is used for the oxidation of ethylenic compounds (see p. 13). It is converted into acetylbenzoyl peroxide by treatment with acetic anhydride (Baeyer and Villiger, *loc. cit.*, p. 1581). A more convenient method of obtaining this substance is by the aerial oxidation of benzaldehyde (see p. 158).

Peroxides and peracids derived from acetic acid and its immediate homologues are less stable than those of the aromatic acids. They were apparently first investigated by Brodie (*J.*, 1864, **17**, 272), who commented on their explosive character.

Acetyl peroxide has been prepared by the action of ethereal acetic anhydride on sodium peroxide (Gambarjan, *loc. cit.*; Nef, *Annalen*, 1897, **298**, 288), or less conveniently by treating acetyl chloride with solid hydrogen peroxide (D'Ans and Friedrich, *Z. anorg. Chem.*, 1911, **73**, 357). In contrast to benzoyl peroxide it bleaches indigo solution and liberates iodine from potassium iodide. Water hydrolyses it to peracetic acid. This acid is best obtained by the action on acetic anhydride of very concentrated hydrogen peroxide containing 1% of sulphuric acid. Distillation of such a mixture under reduced pressure and subsequent freezing of the distillate yields pure peracetic acid (D'Ans and Frey, *Ber.*, 1912, 45, 1848). It is extremely explosive and a vigorous oxidising agent. It attacks cork, rubber, and skin. It oxidises primary aromatic amines to nitroso-compounds and azo-compounds to azoxy-compounds (D'Ans and Kneip, *Ber.*, 1915, **48**, 1141). Its application for the oxidation of ethylenic compounds is referred to on p. 14.

Perpropionic acid and perbutyric acid have been prepared by a similar method. Approximately pure performic acid has been obtained by reaction of formic acid with concentrated hydrogen peroxide containing a trace of sulphuric acid. D'Ans and Frey (*loc. cit.*) describe a simpler method of preparing peracetic acid using boric acetic anhydride.

(5) *Esters.*

(a) *Hydrolysis.*—The formation of esters has already been represented as the result of an equilibrium in the reaction of an acid with an alcohol according to the scheme:

$$\mathrm{R{\cdot}OH + HO{\cdot}CO{\cdot}R' \longrightarrow R'{\cdot}CO{\cdot}OR + H_2O}$$

(R = alkyl. R′ = H, alkyl, aryl, or unsaturated radicle.)

The partial resolution of pure esters into their generators can therefore be effected by treatment with water. With the majority of esters such a process of hydrolysis, if it is to be used for obtaining the pure acid or alcohol, is usually unsatisfactory. Some of them, however, undergo extensive hydrolysis merely by treatment with cold water. This is very marked with methyl and ethyl oxalates, with ethyl formate and with esters of α-hydroxy-acids such as glycollic, lactic, etc. (compare Schreiner, *Annalen*, 1879, **197**, 7; Findlay and Hickmans, *J.*, 1909, **95**, 1004; Findlay and W. E. S. Turner, *ibid.*, 1905, **87**, 747). The esters of the lower α-amino-fatty acids are quantitatively hydrolysed by boiling with an excess of water for several hours under reflux (E. Fischer, *Ber.*, 1901, **34**, 445). β-Alkyl aminobutyric esters are also hydrolysed completely by heating with water (Morsch, *Monatsh.*, 1932, **60**, 61, 65, 68).

It is more usual to effect hydrolysis by heating with the aqueous or aqueous alcoholic solution of an alkali; less commonly with aqueous mineral acid. With the lower alkyl esters of the lower fatty acids and other comparatively simple esters hydrolysis takes place smoothly by heating under reflux with aqueous solutions of sodium or potassium hydroxides. Esters derived from alcohols and acids of comparatively high molecular weight and not appreciably soluble in water are best hydrolysed by alcoholic potash. The procedure is illustrated by the following descriptions.

Hydrolysis of Ethyl Acetate.—The ester (30 g.) is heated under reflux with 120 c.c. of aqueous 20% sodium hydroxide, till the upper layer of ester has dissolved and the odour of the ester has disappeared. The solution is then distilled till a thermometer placed in the neck of the flask shows a temperature of 98—100°.

The distillate is then saturated with potassium carbonate. The alcohol separates as the upper layer, which is removed, dried over potassium carbonate, and distilled.

The alkaline residue from the hydrolysis is evaporated to dryness, after neutralisation with dilute sulphuric acid. The dry solid thus obtained is coarsely ground in a mortar and transferred to a distillation flask. It is then distilled after adding a moderate excess of concentrated sulphuric acid (about 18 c.c.). Acetic acid is collected up to 125°, the fraction 115—125° being collected separately. The first fractions are again distilled, when a further quantity of concentrated acetic acid is obtained.

This process can be employed for the hydrolysis of most esters of comparatively low molecular weight.

Hydrolysis of the Diethyl Ester of Ethylmalonic Acid.—The ester (25 g.) is added gradually to a lukewarm solution of 19 g. of potassium hydroxide in 17 c.c. of water in a round-bottomed flask. The alkaline solution is stirred during the addition of the ester. The mixture soon solidifies to a white solid mass consisting essentially of the potassium salt of the mono-ester of ethylmalonic acid. The mixture is then warmed under reflux till the ester is completely hydrolysed. The solution is cooled, extracted with ether to remove any possible traces of unchanged ester, and then rendered acid to congo paper by the addition of diluted hydrochloric acid (1 : 1).

The liberated ethylmalonic acid is removed from the acid solution by extraction with ether. After drying the ethereal solution with anhydrous sodium sulphate, the solvent is evaporated, leaving approximately pure ethylmalonic acid. After crystallisation from benzene it melts at 111—112°.

This process can be fairly generally applied for the preparation of alkylmalonic acids from the corresponding diethyl esters.

Hydrolysis of Palm Oil.—Melted palm oil (150 g.) is stirred with a solution of 12 g. of sodium hydroxide in 100 c.c. of water and the mixture heated on a water-bath. After about 1 hour, a further amount of 18 g. of sodium hydroxide in 100 c.c. of water is added and the heating and stirring are continued till a portion gives a clear solution in water. The mixture is then diluted to 1,000 c.c. with hot water and acidified by the addition of 110 c.c. of concentrated hydrochloric acid. The solution is boiled till the crude acid forms a transparent layer on the surface of the liquid. It is then allowed to cool, when the layer of crude palmitic acid solidifies. The aqueous layer is separated from the solid acid, neutralised exactly with alkali, and used for the isolation of glycerol (see later).

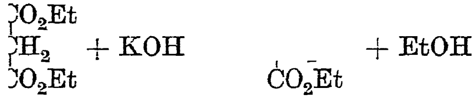
The crude acid is best purified by pressing on porous earthenware or between layers of filter-paper to remove oily impurities, and then crystallising from ethyl alcohol—m. p. 62°.

In order to isolate the glycerol from the aqueous layer, the neutralised solution is concentrated on a water-bath to about half its volume and finally evaporated to dryness under reduced pressure. The solid residue consists essentially of sodium chloride mixed with glycerol. The isolation of the glycerol is effected by two or three extractions with hot absolute alcohol or ethyl acetate. The combined extracts are then distilled at ordinary pressure to remove solvent and then under reduced pressure. Glycerol is collected at 190—195°/12 mm. (yield about 6—8 g.)

In the hydrolysis of natural waxes some difficulty may be encountered in the isolation of the sparingly soluble alcohol, if it is attempted to remove the alkali salt of the fatty acid by treatment with water. The following process, although laborious, avoids this difficulty by precipitating the fatty acid as the sparingly soluble calcium salt.

Hydrolysis of Spermaceti. Isolation of Cetyl Alcohol.—Spermaceti (100 g.) is boiled under reflux for 48 hours with potassium hydroxide (20 g.) dissolved in 50 c.c. of alcohol. The product is then poured into an excess of calcium chloride solution. The precipitate is collected, washed with water, and dried at 30° under reduced pressure. Cetyl alcohol is removed from the dried mass by extracting several times with ethyl alcohol. Evaporation of the alcoholic extracts leaves crude cetyl alcohol, which is purified by boiling with water and subsequent crystallisation from alcohol, m. p. 49—50°.

Many esters of dibasic acids can be hydrolysed to furnish the mono-ester. Thus the diethyl ester of malonic acid yields the potassium salt of the monoethyl ester by treatment with the calculated amount of a cold alcoholic solution of potassium hydroxide.



$$\begin{array}{l} CO_2Et \\ | \\ CH_2 \\ | \\ CO_2Et \end{array} + KOH \qquad \begin{array}{l} | \\ CO_2Et \end{array} + EtOH$$

Preparation of Monoethyl Ester of Malonic Acid.—A solution of 8·7 g. of potassium hydroxide in 100 c.c. of absolute alcohol is added gradually to a well-stirred solution of 25 g. of diethylmalonate in 100 c.c. of absolute alcohol. The mixture is kept at room temperature till its alkaline reaction has disappeared. It is then heated to boiling and filtered hot. Neutral potassium malonate remains on the filter; the filtrate contains the potassium salt of the monoethyl ester of malonic acid, which crystallises out in large flat needles as the filtrate cools. The yield is approximately 70—80% of the weight of ester used.

The free ester acid is obtained by adding concentrated hydrochloric acid to an ice-cold solution of the potassium salt, and subsequently extracting with ether. It is a liquid, b. p. 147°/21 mm. (Freund, *Ber.*, 1884, **17**, 780).

If this process is applied to the preparation of the mono-esters of the alkyl-substituted malonic acids, it must be modified by concentrating the alcoholic filtrate from the hydrolysis under reduced pressure. Otherwise there is no satisfactory separation of the potassium salt of the ester acid owing to its ready solubility in alcohol (Marguery, *Bull. Soc. chim.*, 1905, [iii], 33, 543).

Alkaline hydrolysis may also be used for the estimation of the amount of an ester in a mixture with indifferent products, or for the determination of the purity of an ester. The general conditions are to hydrolyse a known weight of the ester—usually 1—2 g.—by heating under reflux with a known volume of accurately standardised alcoholic potash (approximately 1·0—0·5*N*). After the hydrolysis, the excess of alkali is determined by titration with standard acid, using phenolphthalein as indicator.

A similar process is used for determining the " saponification value " of a fat. This value is defined as the number of mg. of potassium hydroxide required to completely hydrolyse 1 g. of fat. The alcoholic potash required for these determinations is prepared by dissolving 20 g. of potassium hydroxide in an equal volume of water and diluting the solution to 500 c.c. with alcohol. The alcohol required for this purpose must be purified by keeping in contact with powdered potash for several days and then distil immediately before use.

(b) *Alcoholysis.*—Hydrolysis of an ester signifies the replacement of the alcohol residue by hydroxyl; alcoholysis is the exchange of the alcohol residue for another. It is represented by the scheme

$$R{\cdot}CO{\cdot}OR' + R''{\cdot}OH \rightleftarrows R{\cdot}CO{\cdot}OR'' + R'{\cdot}OH$$

This exchange may be achieved by heating the ester with an excess of a suitable alcohol in sealed tubes at a comparatively high temperature (Friedel and Crafts, *Annalen*, 1864, **130**, 198; 1865, **133**, 207; Grün, *Ber.*, 1921, **54**, 294). A more convenient method consists in the action of a small amount of sodium alkoxide dissolved in the appropriate alcohol on the ester. An equilibrium is attained. This reaction was first systematically examined by Purdie and his co-workers (*J.*, 1888, **53**, 391; 1885, **47**, 855; 1887, **51**, 627; *Ber.*, 1887, **20**, 1554), although some isolated observations in the same direction had previously been made (Bouis, *J. pr. Chem.*, 1857, [i], **72**, 308; Claisen, *Ber.*, 1887, **20**, 646). Alcoholysis succeeds with esters of saturated fatty acids, aromatic acids, and unsaturated acids. It is effected by shaking at room temperature, a solution of the ester in about ten times its weight of a suitable primary alcohol containing a small amount of dissolved sodium or potassium. For the successful replacement of alcohol residues by *sec.*- and *tert.*-alcohols the reaction mixture must be heated (M. Reimer and Downes, *J. Amer. Chem. Soc.*, 1921, **43**, 945; Pfannl, *Monatsh.*, 1910, **31**, 301; 1911, **32**, 513; Sudborough and Karve, *J. Ind. Inst. Sci.*, 1919, **3**, 1; Dasannacharya and Sudborough, *ibid.*, 1921, **4**, 181; Kolhatkar, *J.*, 1915, **107**, 921; Shimomura and Cohen, *ibid.*, 1922, **121**, 884, 2051).

Alcoholysis of Glycol Diacetate; Formation of Glycol and Ethyl Acetate.—Glycol diacetate (7·3 g.) is added to absolute alcohol (50 c.c.) in which 0·1 g. of sodium has been dissolved. The odour of ethyl acetate is observed almost immediately. The reaction is completed by heating under reflux for 6 hours on a steam-bath, when the reaction mixture is fractionally distilled. Pure glycol is collected at 190—200°—yield 75—85% of theory (Bainbridge, *J.*, 1914, **105**, 2297)

Trimethylene glycol is obtained similarly in 30% yield from the corresponding acetate. Propylene glycol diacetate and $\alpha\gamma$- and $\beta\gamma$-butane diacetates, however, do not yield the corresponding glycols by use of such dilute solutions of ethoxide; a higher concentration of sodium ethoxide is necessary.

Preparation of Mannitol from Mannitol Hexa-acetate by Alcoholysis.—Mannitol hexa-acetate (8 g.) is heated with 20 c.c. of methyl alcohol on a water-bath and then 2 c.c. of 0·1*N*-solution of sodium methoxide are added. After a few minutes mannitol commences to separate. The mixture is evaporated to dryness under reduced pressure, the residue dissolved in 5 c.c. of water, and 25 c.c. of warm absolute alcohol are added. Mannitol separates on cooling, m. p. 165°—yield 2·7 g. (Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613).

A similar process has been applied for the preparation of sucrose from its octa-acetate and for obtaining glucosides from their acetates.

Exchange between glycols, glycerol, and monohydric alcohols has been effected also by the catalytic affect of small amounts of potassium carbonate (E. Fischer, *Ber.*, 1920, **53**, 1634).

(c) *Formation of Amides.*—The replacement of the alkoxy-group of esters by amino-groups by reaction of the esters with ammonia or amines is discussed on p. 199.

(d) *Condensation of Esters.*—The esters of carboxylic acids condense, under the influence of appropriate reagents, with a $-CH_2-$ group, which is activated by an adjacent $>CO$ group or $-CN$ group or by two adjacent double bonds. Substances generally capable of condensing with esters are ketones and carboxylic esters. This type of condensation is very important, since it affords a general method of preparing β-ketonic esters and 1 : 3-diketones according to schemes I and II.

$$R{\cdot}CO{\cdot}OEt + R'{\cdot}CH_2{\cdot}CO{\cdot}OEt \rightarrow R{\cdot}CO{\cdot}CHR'{\cdot}CO{\cdot}OEt + EtOH \quad \text{(I.)}$$

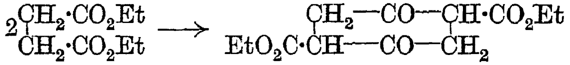
$$R{\cdot}CO{\cdot}OEt + CH_3{\cdot}CO{\cdot}R' \rightarrow R{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}R' + EtOH \quad \text{(II.)}$$

The production of ethyl acetoacetate from ethyl acetate is the best-known condensation of type (I). Metallic sodium or sodium ethoxide are the most important condensing agents; sodamide has also been used.

Preparation of Ethyl Acetoacetate.—Sodium wire (100 g.) is covered by 1 kg. of pure dry ethyl acetate. The reaction commences only after keeping at room temperature for some minutes. It then becomes vigorous, and no attempt should be made to check it. It is completed by heating in an oil-bath till all the metal has dissolved. A 50% solution of acetic acid (555 g.) is poured into the reaction mixture while it is still fluid, and after cooling it is diluted with 500 c.c. of water. After a thorough mixing, the upper layer is separated, washed with a little water, and then freed from the greater part of the unchanged ester by distillation on a water-bath. The residue is fractionally distilled under reduced pressure. The yield of ester, b. p. 74°/15 mm., is about 175 g. (J. Wislicenus, *Annalen*, 1877, **186**, 210; compare Snell and McElvain, *J. Amer. Chem. Soc.*, 1931, **53**, 750).

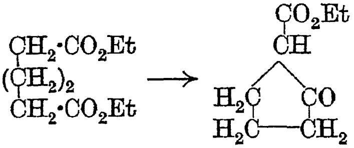
The esters of the immediate homologues of acetic acid also undergo a similar condensation in presence of sodium or sodium ethoxide, if a $-CH_2$ is adjacent to the carboxalkoxy-group. Thus ethyl propionate yields propionylpropionic ester, $C_2H_5{\cdot}CO{\cdot}CH(Et){\cdot}CO{\cdot}OEt$; *n*-butyric and *iso*valeric esters and the higher homologues behave similarly (Hantzsch and Wohlbrück, *Ber.*, 1887, **20**, 1320; Wohlbrück, *ibid.*, p. 2332; McElvain, *J. Amer. Chem. Soc.*, 1929, **51**, 3124; Briese and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1697). The yields of β-ketonic esters from these esters are lower than those from ethyl acetate. According to Dieckmann (*Ber.*, 1900, **33**, 2760) this is probably due to the α-alkyl-substituted β-ketonic ester reverting to its generators under the influence of sodium ethoxide. Methoxyacetic ester, however, condenses smoothly to give αγ-dimethoxyacetoacetic ester under the influence of sodium ethoxide (Pratt and Robinson, *J.*, 1925, **127**, 168). Briese and McElvain (*loc. cit.*) claim that esters of propionic acid and its higher homologues furnish good yields of the corresponding α-alkyl β-keto-esters if the condensation is effected by sodium ethoxide under reduced pressure.

Diethylsuccinate suffers condensation in presence of sodium to furnish a diketonic ester—succinyl succinic ester (XIV)—by a process analogous in type to the acetoacetic ester condensation (Herrmann, *Annalen,* 1882, **211**, 306). The esters of those homologues of succinic acid containing 6, 7, or 8 atoms of carbon undergo internal condensation to furnish cyclic keto-esters. Thus adipic ester (XV) yields (XVI). Pimelic and suberic esters (XVII) and (XVIII) behave similarly

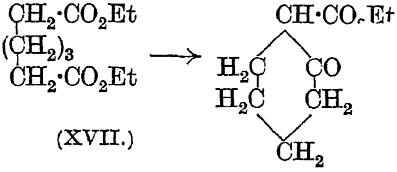


$$2\begin{array}{l}CH_2\cdot CO_2Et\\ CH_2\cdot CO_2Et\end{array} \longrightarrow \begin{array}{l}\quad\;\; CH_2-CO-CH\cdot CO_2Et\\ EtO_2C\cdot CH-CO-CH_2\end{array}$$

(XIV.)

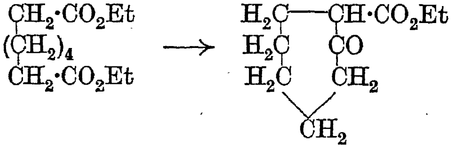


(XV.) (XVI.)



(XVII.) (XIX.)

(XVIII.)



(XX.)

The esters of glutaric, sebacic, and azelaic acids do not yield any appreciable quantity of keto-esters by condensation (Dieckmann, *Annalen,* 1901, **317**, 27; *Ber.*, 1894, **27**, 102).

Preparation of Ethyl Ester of 2-Ketocyclopentane Carboxylic Acid (XVI).—After adding successively to 20 g. of ethyl adipate a few drops of alcohol and 4·6 g. of sodium wire, the temperature of the mixture is gradually raised by heating in an oil-bath. At about 100—110° a vigorous reaction sets in, and the whole soon becomes converted into a yellowish solid mass. After heating at 120—140° for about ½ hour, the mass is cooled and disintegrated. It is then covered by ether and acidified by the cautious addition of dilute sulphuric acid. The ethereal layer is separated, washed with dilute sodium carbonate solution, and dried over anhydrous sodium sulphate. Evaporation of the solvent leaves the crude keto-ester. It is purified by distillation under reduced pressure, b. p. 103—104°—yield 60% of theory (Dieckmann, *Annalen,* 1901, **317**, 51).

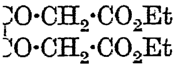
Condensation may be effected between two different esters to yield β-ketonic esters by the action of sodium or sodium alkoxides. It is obvious that for practical purposes one of the components must react rapidly and preferably be incapable of self-condensation. Thus formic and oxalic esters and, to a less extent, benzoic esters are used for this purpose. Oxalic ester condenses with ethyl acetate in presence of sodium to furnish oxalacetic ester (XXI) (W. Wislicenus, *Ber.*, 1886, **19**, 3225); with propionic ester to yield α-methyloxalacetic ester (XXII) (Arnold, *Annalen,* 1888, **246**, 329) and with phenylacetic ester to furnish α-phenyloxalacetic ester (XXIII) . Wislicenus, *Ber.*, 1887, **20**, 590).

$EtO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$ (XXI.)

$EtO_2C{\cdot}CO{\cdot}CH(Me){\cdot}CO_2Et$ (XXII.)

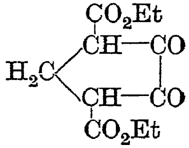
$EtO_2C{\cdot}CO{\cdot}CH(Ph){\cdot}CO_2Et$ (XXIII.)

Oxalic ester can also be made to condense with 2 molecules of a suitable ester; with acetic ester it can yield ketipinic ester (XXIV) (Wislicenus, *Ber.*, 1887, **20**, 590); with glutaric ester it furnishes the cyclic diketo ester (XXV) (Dieckmann, *Ber.*, 1897, **30**, 1470). Formic ester similarly reacts with phenylacetic ester yielding formylphenylacetic ester (XXVI) (Wislicenus, *Ber.*, 1887, **20**, 2930).



$$\begin{array}{l} CO{\cdot}CH_2{\cdot}CO_2Et \\ | \\ CO{\cdot}CH_2{\cdot}CO_2Et \end{array}$$

(XXIV.)



(XXV.)

$OHC{\cdot}CH(Ph){\cdot}CO_2Et$

or

$HO{\cdot}CH{:}C(Ph){\cdot}CO_2Et$

(XXVI.)

Preparation of Oxalacetic Ester.—One atomic proportion of sodium wire is added to ethyl oxalate diluted with four times its volume of dry ether, and then rather more than the calculated amount of dry ethyl acetate is added gradually. The metal gradually dissolves with the evolution of hydrogen, and the reaction mixture, after several hours, is converted into a yellowish crystalline paste of the sodium salt of oxalacetic ester. After keeping for several hours the precipitate is collected by filtration and washed with ether. Oxalacetic ester is isolated from the pure sodium salt thus obtained, by covering it with water and cautiously acidifying with dilute hydrochloric acid. The ester is taken up in ether, and after washing the ethereal solution and drying, it is fractionally distilled under reduced pressure, b. p. 131—132°/24 mm. (Wislicenus, *Annalen*, 1888, **246**, 315).

Preparation of Formylphenylacetic Ester (XXVI).—Equimolecular proportions of ethyl formate and of ethyl phenylacetate are added to a suspension of freshly-prepared dry sodium ethoxide in three times its weight of dry ether. The mixture is kept for several days in a closed flask and then ice-water added. After shaking, the aqueous layer is separated and acidified with dilute hydrochloric acid. The oil which separates is taken up in ether, the ethereal solution washed with dilute sodium carbonate solution, dried, and the solvent evaporated. The residue is a mixture of keto- and enol forms. The solid keto-form is collected by filtration, while distillation of the filtrate under reduced pressure yields the pure enol form, b. p. 144—145°/16 mm. The pure keto-form melts at 69—71° (W. Wislicenus, *Ber.*, 1887, **20**, 2930).

The esters of carboxylic acids can condense with ketones of the general form $R{\cdot}CO{\cdot}CH_3$ to yield 1 : 3-diketones. The condensation is effected either by sodium or by sodium ethoxide suspended in ether; less rarely by sodamide. The reaction was developed by Claisen. More recently it has been employed extensively by Morgan and his co-workers for the preparation of a large number of 1 : 3-diketones. The condensation is illustrated by the following descriptions.

Preparation of Acetyl Acetone (method 1).—Pure dry ethyl acetate (900 c.c.) is added to 100 g. of sodium wire covered by a layer of ether in a 4—5-l. flask. The flask is cooled in a freezing mixture during the addition of the ester. Dry acetone (314 g.) is now added gradually, care being taken not to add a further quantity of acetone till the reaction due to the previous quantity has moderated. When all the acetone has been added, the reaction mixture is kept at 0° for several hours, and then at room temperature for 12 hours. The sodium salt which has separated during this period is dissolved by the addition of 1500 c.c. of ice-water. The aqueous layer is separated, and acidified by adding dilute acetic acid. The addition of copper acetate * solution now precipitates the copper salt of acetyl acetone, which, after keeping for some time, is filtered under suction.

Treatment of the copper salt with acid yields the free diketone. This is brought about as follows. The moist copper salt is suspended in ether and diluted sulphuric acid (20% concentration) added. The mixture is shaken till the solid has dissolved. The ethereal layer is then separated, dried over calcium chloride, and after distilling off the ether through a column, the residue of diketone is fractionated. Crude acetyl acetone is collected at 125—140°—yield 160—170 g. The pure diketone boils at 139°/746 mm. (Claisen, *Annalen*, 1893, **277**, 168).

(Method 2.)—Finely-powdered sodamide (34 g.) is added gradually to a mixture of 120 c.c. of ethyl acetate and 32 c.c. of acetone cooled in a freezing mixture. A strong evolution of ammonia commences immediately, and the mixture is kept at 0° for several hours and then at room temperature for 12 hours. The reaction product is treated with ice-water as described in the preceding preparation. The subsequent operations are the same (Claisen, *Ber.*, 1905, **38**, 694).

Preparation of Propionyl Acetone.—Methyl ethyl ketone (42 c.c.) is added slowly and with vigorous shaking to a mixture of 11 g. of sodium wire and 190 c.c. of ethyl acetate cooled to 0°. After 12 hours, the mixture is heated on a water-bath for 1½ hours, then cooled and poured on crushed ice. The ethereal layer is separated and washed twice with water. The combined aqueous layers are neutralised with dilute acetic acid and treated with the necessary amount of *N*/8-cupric acetate solution. The precipitate of pale blue copper propionyl acetone is dried at 80°, after washing with water. Yield 49% of theory, m. p. 197—198°.

Propionyl acetone is obtained by decomposing the copper salt with dilute sulphuric acid in presence of ether. Fractional distillation of the ethereal solution, after the usual operations of washing and drying, yields pure propionyl acetone, b. p. 158° (Morgan and Reeves, *J.*, 1923, **123**, 447).

A somewhat similar procedure has been employed for the preparation of other β-diketones by the condensation of ketones of the type $CH_3{\cdot}CO{\cdot}R$ (where R = propyl, butyl, amyl, nonyl, undecyl) with esters of fatty acids such as acetic, propionic, butyric, and phenyl acetic (Morgan and Drew, and Ackermann, *J.*, 1924, **125**, 740; Morgan and Thomason, *ibid.*, p. 756; Morgan and Holmes, *ibid.*, p. 760; Morgan and Porter, *ibid.*, p. 1271; Morgan and Taylor, *ibid.*, 1925, **127**, 2620; Morgan and E. Jones, *ibid.*, p. 2619; Claisen and Ehrhardt, *Ber.*, 1889, **22**, 1009).

The application of this condensation between esters and ketones of the general type $R{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}R$ with the object of preparing diketones of the type $R{\cdot}CO{\cdot}CHR{\cdot}CO{\cdot}R'$ does not proceed smoothly. Morgan, Drew, and Porter (*Ber.*, 1925, **58**, 336) have found that, in general, a small yield of the substituted diketone is obtained if the reaction is brought about at 0°. If the reaction mixture is heated, little or none of the required substance is obtained. These results are quite analogous to the behaviour of esters of homologues of acetic acid in the acetoacetic ester condensation. It is not unlikely that the grouping $-CO{\cdot}CHR{\cdot}CO-$ is less stable to alcoholic ethoxide than the grouping $-CO{\cdot}CH_2{\cdot}CO-$.

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* Copper acetate solution is prepared by warming 500 g. of copper acetate in 5—6 litres of water for some hours, and filtering from undissolved basic salt. While still warm it is added to the acidified product of the condensation.

Preparation of Phenyl Acetyl Acetophenone.—Sodium wire (23 g.) is added to a well-cooled solution of 250 g. of phenylacetic ester and 120 g. acetophenone in 500 c.c. of dry ether. The mixture is kept at 0° for some time and then at room temperature. The reaction is completed by raising the temperature gradually and by finally heating under reflux on a water-bath till all the sodium has reacted. After cooling, the mixture is rendered slightly acid with acetic acid and then shaken with a saturated solution of copper acetate. The copper salt which separates is collected and decomposed with dilute sulphuric acid in presence of ether. The pure diketone is obtained in approximately 50% yield—m. p. 54—56° (Bülow and Grotowsky, *Ber.*, 1901, **34**, 1479).

Preparation of Benzoyl Acetone (method 1).—Acetophenone (1 mol. prop.) is added to a mixture of dry ethyl acetate (1 mol. prop.) and dry sodium ethoxide (1 mol. prop.) cooled by an external bath of ice. The mixture at first liquefies and later sets to a microcrystalline paste of light yellow needles of the sodium salt of benzoyl acetone. The salt is collected by filtration and subsequently acidified with dilute acetic acid. Pure benzoyl acetone melts at 60—61° (Claisen, *Ber.*, 1887, **20**, 2180).

(Method 2.)—Finely-divided sodamide (16 g.) is added gradually to a solution of 24 g. of acetophenone and 19 g. of ethyl acetate in 150 c.c. of ether cooled by an external bath of ice. After keeping for about 1 hour the whole has been converted into a thick paste of the sodium salt of benzoyl acetone. After keeping for 24 hours, the salt is dissolved by the addition of water and the ether layer separated. Ether dissolved in the aqueous solution is removed by a stream of air. Benzoyl acetone is precipitated from the aqueous solution by acidifying with acetic acid—yield 25 g. (Claisen, *Ber.*, 1905, **38**, [illegible]

Oxalic ester condenses with ketones of the type $CH_3{\cdot}CO{\cdot}R$ in a manner analogous to the esters of the fatty acids, giving diketo-esters of the type $R{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CO{\cdot}OEt$ (Claisen and Stylos, *Ber.*, 1888, **21**, 1141; 1887, **20**, 2188; Brömme and Claisen, *Ber.*, 1888, **21**, 1131).

Preparation of Oxalacetone.—A mixture of equimolecular proportions of acetone (58 g.) and diethyl oxalate (146 g.) is added to a well-cooled alcoholic solution of sodium ethoxide prepared by dissolving 23 g. of sodium in 550 c.c. of absolute alcohol. The sodium salt of oxalacetone commences soon to separate, and after keeping the reaction mixture for 24 hours the sodium salt is collected by filtration. The free keto-ester is obtained by stirring the sodium salt with ice-water and then acidifying with a slight excess of dilute sulphuric acid. The free ester is taken up in ether. Evaporation of the dried ethereal solution followed by distillation under reduced pressure gives pure oxalacetone, b.p. 113—116°/19 mm.—yield 100 g. (Claisen and Stylos, *Ber.*, 1887, **20**, 2188).

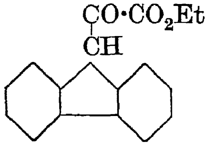
Condensation of formic esters with ketones leads to formyl derivative of the type $R{\cdot}CO{\cdot}CH_2{\cdot}CHO$ or $R{\cdot}CO{\cdot}CH{:}CH{\cdot}OH$. The keto-form is a β-ketoaldehyde. The majority of formyl derivatives exist largely as enols. Like the formyl derivatives of esters, they tend to polymerise (Claisen and L. Fischer, *Ber.*, 1887, **20**, 2191; Claisen and Meyerowitz, *ibid.*, 1889, **22**, 3273).

Preparation of Phenyl β-Hydroxyvinyl Ketone, (Ph·CO·CH:CH·OH).—A mixture of acetophenone (60 g.) and ethyl formate (40 g.) is added slowly to a suspension of dry sodium ethoxide (35 g.) in 100 g. of ether, cooled by an external bath of ice. The sodium salt of the hydroxy-ketone soon commences to separate (yield 90% of the weight of acetophenone). It is collected by filtration, dissolved in ice-water, rendered faintly acid by the addition of acetic acid, and then a slight excess of a solution of cupric acetate added. The copper salt of the hydroxy-ketone is obtained as an olive-green precipitate. The free hydroxy-ketone may be obtained from the salt by treatment with dilute sulphuric acid in presence of ether (Bülow and v. Sicherer, *Ber.*, 1901, **34**, 3891).

Preparation of p-*Anisyl β-Hydroxyvinyl Ketone.*—A solution of *p*-acetylanisole (10 g.) in 7·4 g. of ethyl formate is introduced in small portions at a time, and with constant stirring, to a suspension of sodium ethoxide in ether.[*] The reaction mixture is cooled in a bath of ice and is kept overnight in an ice-chest. It is then treated with ice and water, more ether added, and just sufficient acetic acid to give an acid reaction. The ethereal layer is separated and shaken with an excess of a saturated solution of copper acetate. A pale green copper salt is precipitated. It is collected by filtration, washed with ether and water, and then dried. The copper salt separates from chloroform in flat green prisms, m. p. 206—207°.

An ethereal solution of the free hydroxyvinyl ketone may be obtained by shaking a suspension of the copper salt in ether with dilute sulphuric acid and ice-water (Pratt, Robinson, and Williams, *J.*, 1924, **125**, 202).

The methylene group situated between two doubly-linked carbon atoms, as in *cyclo*pentadiene, indene, and fluorene, is sufficiently reactive to condense with ethyl oxalate under the influence of alkoxides. Thus fluorene yields (XXVII) (Thiele, *Ber.*, 1900, **33**, 666, 851; W. Wislicenus, *ibid.*, p. 771; compare W. Wislicenus, *Annalen*, 1924, **436**, 1).



(XXVII.)

Although ethyl acetate undergoes condensation smoothly in the presence of sodium to yield ethyl acetoacetate, the reaction takes another course if it is effected by 2 atomic proportions of sodium acting on 1 molecular proportion of the ester dissolved in dry ether or benzene. The product is acetoin, CH_3·CO·CH(OH)·CH_3. The yield is better with homologues of acetic acid. The reaction has been examined for esters of propionic, butyric, caproic, and pivalic acids (Bouveault and Locquin, *Bull. Soc. chim.*, 1906, [iii], **35**, 629).

[*] The suspension of sodium ethoxide required for this preparation is obtained by granulating 1·6 g. of sodium under toluene, pouring away the toluene, and washing the sodium with a little dry ether. A solution of 3·2 g. of ethyl alcohol in 50 c.c. of dry ether is added. When the formation of ethoxide is complete, the reactants are added.

(d) *Reaction with the Grignard Reagent.*—The carbethoxy-group of esters reacts with the Grignard reagent to furnish tertiary alcohols according to the scheme

$$R\cdot CO_2Et + 2RMgBr \longrightarrow EtOMgBr + R_3COMgBr \xrightarrow{H_2O} R_3C\cdot OH$$

Although a ketone is an intermediate product in this reaction, the method does not appear to be of any practical value for the preparation of ketones, owing to the difficulty of stopping it at this stage. On the other hand, it has received considerable application for the preparation of tertiary alcohols. The general conditions are illustrated by the following descriptions.

Preparation of Dimethylethyl Carbinol.—Ethyl propionate (31 g.) diluted with its own volume of ether is added gradually to an ethereal solution of methyl magnesium iodide prepared from 84 g. of methyl iodide (see p. 374). The reaction mixture is cooled and stirred during the addition of the ester, and is contained in a round-bottomed flask fitted with a reflux condenser provided with a guard tube containing calcium chloride. After keeping overnight, crushed ice and dilute sulphuric acid are added to the product. The ethereal solution is separated and the aqueous layer extracted twice with ether. The combined ethereal solutions are washed with dilute sodium carbonate solution and water and then dried in contact with potassium carbonate. Fractional distillation of the solution furnishes dimethylethyl carbinol, b. p. 100—102°.

Preparation of Triphenyl Carbinol.—Dry ethyl benzoate (20 g.) diluted with its own volume of ether is added gradually to a cooled ethereal solution of phenyl magnesium bromide from 57 g. of bromobenzene. When all the ester has been added, the mixture is gently warmed under reflux for 1 hour with frequent shaking. The product is then treated with a saturated aqueous solution of ammonium chloride and crushed ice, and then steam distilled. Triphenyl carbinol remains as a solid in the distillation flask. It is collected by filtration, washed with water, and crystallised from hot alcohol, m. p. 162°—yield 25—30 g.

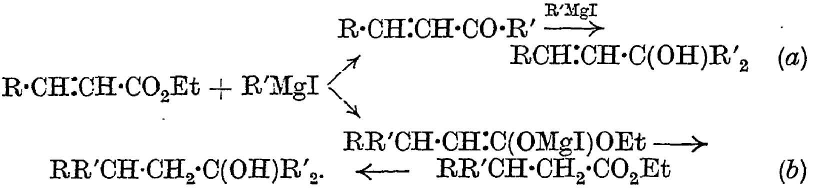
It must be noted that when the tertiary alcohol formed in this reaction tends to eliminate the elements of water the product may be an olefin (compare Stadnikoff, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 2115).

The reaction of the Grignard reagent with esters of formic acid follows the same course as that indicated above, but owing to the structure of formic esters, the product is a secondary alcohol.

$$H\cdot CO_2Et + 2RMgI \longrightarrow R_2CH\cdot OMgI + EtOMgI \xrightarrow{H_2O} R_2CH\cdot OH$$

The esters of succinic acid and its homologues and of oxalic acid and *iso-* and *tere*-phthalic acids react normally with Grignard reagents to furnish as the principal product a ditertiary glycol. However, by modifying the experimental conditions, using magnesium, alkyl iodide, and the ester in ethereal solution, only one carbalkoxy-group may be attacked with the formation of the ester of a hydroxy-acid (Hepworth, *J.*, 1919, **115**, 1203). The reaction of esters of malonic and phthalic acids in general gives rise to abnormal products.

The course of the reaction of αβ-unsaturated esters with Grignard reagents appears to depend to some extent, on the nature of the reactants. The main products to be expected are (*a*) an unsaturated tertiary alcohol or unsaturated ketone by a normal reaction with the carbalkoxy group (equation *a*); (*b*) a saturated ketone or tertiary alcohol due to the initial addition of the Grignard reagent to the double bond (Kohler, *Amer. Chem. J.*, 1905, **34**, 132; Kohler and Heritage, *ibid.*, 1905, 33, 21, 153).

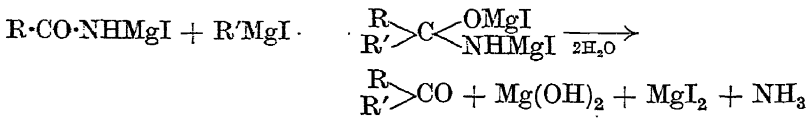


$$\mathrm{R{\cdot}CH{:}CH{\cdot}CO_2Et + R'MgI} \nearrow \mathrm{R{\cdot}CH{:}CH{\cdot}CO{\cdot}R'} \xrightarrow{\mathrm{R'MgI}} \mathrm{RCH{:}CH{\cdot}C(OH)R'_2} \quad (a)$$

$$\mathrm{R{\cdot}CH{:}CH{\cdot}CO_2Et + R'MgI} \searrow \mathrm{RR'CH{\cdot}CH{:}C(OMgI)OEt} \longrightarrow \mathrm{RR'CH{\cdot}CH_2{\cdot}CO_2Et} \longrightarrow \mathrm{RR'CH{\cdot}CH_2{\cdot}C(OH)R'_2} \quad (b)$$

The reaction of Grignard reagents with other carboxylic derivatives is of less importance. Thus with acyl chlorides the reaction proceeds through the intermediate formation of a ketone with the formation of a tertiary alcohol as the final product. It has been possible in some instances to stop the reaction at the ketone stage (Acree, *Ber.*, 1904, **37**, 628; Oddo, *ibid.*, 1910, **43**, 1012), but in general this type of reaction is effected more conveniently by the use of zinc alkyl halides (see p. 375).

The formation of ketones can also be effected by treating acid amides with an excess of the Grignard reagent. The yields, however, appear to depend on the amide used; amides of the higher fatty acids give better yields than do those of the lower fatty acids (Béis, *Compt. rend.*, 1903, **137**, 575; Ryan and Nolan, *Proc. Roy. Irish Acad.*, 1912, **30**, *B*, 1). A somewhat more complicated example of this reaction is the formation of optically active benzoins from optically active mandelamides (McKenzie and Wren, *J.*, 1908, **93**, 310; Wren, *ibid.*, 1909, **95**, 1583). The reaction probably proceeds according to the following equations :



$$\mathrm{R{\cdot}CO{\cdot}NH_2 + R'MgI} \cdots \mathrm{R{\cdot}CO{\cdot}NH{\cdot}MgI + R'H}$$

$$\mathrm{R{\cdot}CO{\cdot}NHMgI + R'MgI} \cdots {}^{\mathrm{R}}_{\mathrm{R'}}\!\!>\!\mathrm{C}\!<\!{}^{\mathrm{OMgI}}_{\mathrm{NHMgI}} \xrightarrow[\mathrm{2H_2O}]{} {}^{\mathrm{R}}_{\mathrm{R'}}\!\!>\!\mathrm{CO + Mg(OH)_2 + MgI_2 + NH_3}$$

Some acid anhydrides also yield ketones by reaction with 1 molecular proportion of Grignard reagent (Fournier, *Bull. Soc. chim.*, 1910, [iv], **7**, 836), but using 2 molecular proportions of the reagent, tertiary alcohols are formed.

(6) *Reduction of Carboxylic Acids, their Esters, Chlorides, and Anhydrides to Aldehydes and Alcohols.*

The free carboxylic acids do not readily yield either aldehydes or alcohols by the ordinary methods of reduction. Exceptions to this generalisation appear to be *o*-hydroxy aromatic acids. Thus, it has been known for some time that salicylic acid is reduced by an excess of sodium amalgam to *o*-hydroxybenzyl alcohol (v. d. Velden, *J. pr. Chem.*, 1877, [ii], **15**, 163). The reduction to aldehyde takes place in presence of boric acid and sufficient sulphite to combine with the aldehyde as it is formed. The sulphite may be replaced by *p*-toluidine. This method succeeds with salicylic acid, the cresotic acids, α-naphthol-2-carboxylic acid, and some of their substitution products. Di- and tri-hydroxybenzoic acids either are not reduced or give only poor yields. It is noteworthy that the hydroxyl of β-naphthol-3-carboxylic acid is reduced simultaneously with the carboxyl to give tetrahydronaphthaldehyde. The yield is, however, only 25% of the theoretical (Weil, *Ber.*, 1908, **41**, 4147; Weil and Ostermeier, *ibid.*, 1921, **54**, 3217; Weil and Heerdt, *ibid.*, 1922, **55**, 224; Weil and Brimmer, *ibid.*, p. 301; Weil, Traun, and Marcel, *ibid.*, p. 2664).

The following description illustrates the process.

Preparation of Salicylaldehyde.—Salicylic acid (15 g.) is exactly neutralised by the addition of an aqueous solution of sodium carbonate. The solution is diluted to 1 litre, heated, and then 18 g. of *p*-toluidine are added. As the resulting solution cools, it is vigorously stirred in order to obtain the base in as fine a state of division as possible. After the addition of 250 g. of salt and 15 g. of boric acid, the reduction is brought about by gradually adding 2% sodium amalgam (about 330—430 g. are required). Boric acid is added at intervals to keep the solution faintly acid, and the reduction mixture is stirred throughout the operation. The reduction is complete when a portion of the solution gives no precipitate of salicylic acid when acidified with dilute hydrochloric acid. The product separates as salicylidene *p*-toluidine. The aldehyde is obtained free by acidifying the reaction mixture with an excess of dilute hydrochloric acid and distilling in steam. The aldehyde is extracted from the distillate by ether—yield 7—8 g. (Weil, *Ber.*, 1908, **41**, 4147).

A few other examples of the reduction of acids, their chlorides, and anhydrides to alcohols or aldehydes by means of sodium amalgam or zinc and acid are recorded in the literature. Thus Linnemann (*Annalen*, 1872, **161**, 178) describes the production of *n*-butyl alcohol by the reduction of a mixture of *n*-butyryl chloride and butyric acid, or a mixture of the anhydride and free acid by means of sodium amalgam. The yields are poor, averaging less than 10% of the theoretical. J. Wislicenus (*Ber.*, 1884, **17**, 2178) has reduced phthalic anhydride to phthalide by zinc and hydrochloric acid.

The electro-reduction of acids has been examined. By this means, and under appropriate conditions, many aromatic acids furnish the corresponding alcohols. The original papers should be consulted for experimental conditions (Tafel and Friedrichs, *Ber.*, 1904, **37**, 3187; Mettler, *ibid.*, 1905, **38**, 1745; 1906, **39**, 2933; Marie, Marquis, and Birkenstock, *Bull. Soc. chim.*, 1919, [iv], **25**, 512).

The conversion of fatty acids into the corresponding aldehydes may be effected by passing the vaporised acid mixed with formic acid over titanium dioxide at 250—300°. The aldehyde is formed in yields of 50% and more from acetic acid and its homologues and also from phenylacetic acid. If thoria is used as the catalyst, the yields are smaller (Sabatier and Mailhe, *Compt. rend.*, 1912, **154**, 561).

An older method, which, however, does not usually give good results, consists in heating an intimate mixture of the calcium salt of the acid with calcium formate.

It has been shown recently that acyl chlorides may be reduced to the corresponding aldehyde catalytically by hydrogen in presence of palladised barium sulphate or kieselguhr. The hydrogenation is brought about in boiling xylene or cumene solution with a regulator such as quinoline, which has been heated with one-sixth of its weight of sulphur for several hours. The regulator appears to prevent reduction of the aldehyde to alcohol or even to hydrocarbon. The method has been applied successfully to the reduction of anisoyl chloride, benzoyl chloride, nitro- and chloro-benzoyl chlorides, butyryl and stearyl chlorides. Cinnamoyl chloride yields cinnamyl aldehyde without any appreciable reduction of the double bond. Suberyl and sebacyl chlorides and the chlorides of *iso*- and *tere*-phthalic acids also yield the corresponding dialdehydes by this process (Rosenmund, *Ber.*, 1918, **51**, 585; Rosenmund and Zetzsche, *ibid.*, 1921, **54**, 425, 638, 2038, 2888; Rosenmund and Pfankuch, *ibid.*, 1922, **55**, 2360; Rosenmund and Zetzsche, *ibid.*, 1923, **56**, 1481).

The formation of some aldehydes from carboxylic acids can be effected by converting the acid into the anilide and then by treatment with phosphorus pentachloride into the corresponding iminochloride (p. 225), which by treatment with stannous chloride under suitable conditions yields an azomethine. Hydrolysis of the last product furnishes the required aldehyde (Sonn and E. Müller, *Ber.*, 1919, **52**, 1927). Thus the preparation of benzaldehyde from benzoic acid requires the following stages by this method :

$$\mathrm{Ph{\cdot}CO_2H} \longrightarrow \mathrm{Ph{\cdot}CONHPh} \xrightarrow{\mathrm{PCl_5}} \mathrm{Ph{\cdot}CCl{:}NPh} \xrightarrow{\mathrm{SnCl_2}}$$

$$\mathrm{Ph{\cdot}CH{:}NPh} \xrightarrow{\text{hydrolysis}} \mathrm{Ph{\cdot}CHO} + \mathrm{Ph{\cdot}NH_2}$$

Preparation of Benzaldehyde from Benzoic Acid.—The reducing agent for this purpose is prepared by passing dry hydrogen chloride into a suspension of dry powdered stannous chloride (70 g.) in 350 c.c. of dry ether till the salt dissolves. Freshly prepared benzanilide iminochloride (25 g.) is added to this solution and the mixture shaken mechanically. It soon separates into two layers, the lower, which is dark yellow and viscous, gradually depositing crystals; eventually it solidifies. After 2 hours, it is collected by filtration and washed with dry ether—yield 46 g.

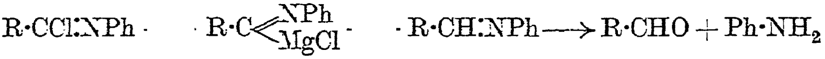
The product, which is a double salt of the azomethine and tin chloride, is hydrolysed by adding 50 c.c. of dilute hydrochloric acid to 40 g. of the double salt and then steam distilling. Benzaldehyde is separated from the distillate by means of ether—yield 10·5 g.

Cinnamaldehyde is similarly prepared by the reduction of cinnamphenyliminochloride (see p. 225) (Sonn and Müller, *loc. cit.*).

Preparation of p-*Hydroxybenzaldehyde.*—*p*-Carbethoxybenzophenyliminochloride (10 g.) (see p. 226) in 150 c.c. of dry ether is mixed with a solution of

20 g. of anhydrous stannous chloride in 100 c.c. of ether saturated with hydrogen chloride. After shaking for several hours, the tin double salt is collected. It is hydrolysed by warming 10 g. with 75 c.c. of 20% sulphuric acid for a short time. The brownish flocculent mass which separates is collected by filtration and washed with water. 5 G. of this product are dissolved in 30 c.c. of alcohol and heated on a water-bath with the addition of the calculated amount of 33% potassium hydroxide till it is completely soluble in water. The alcohol is then removed by distillation and the residue diluted with 50 c.c. of water. On acidification *p*-hydroxybenzaldehyde separates, and further amounts are obtained by extracting the aqueous solution with ether. The product is purified by repeated crystallisation from water with the addition of decolorising charcoal (Sonn and Müller, *loc. cit.*).

Another method of very limited application for effecting the reduction of carboxylic acids to the corresponding aldehydes has been described by Staudinger (*Ber.*, 1908, **41**, 2217). It is based on the following series of reactions :



$$R{\cdot}CCl{:}NPh \cdot \qquad \cdot R{\cdot}C{<}^{NPh}_{MgCl} \cdot \qquad \cdot R{\cdot}CH{:}NPh \longrightarrow R{\cdot}CHO + Ph{\cdot}NH_2$$

An alternative method consists in converting the acid into the nitrile and thence into the aldehyde by a method described on p. 253.

The preparation of the corresponding alcohols from acids can be effected, often in good yield, by reduction of the esters by means of sodium and ethyl or amyl alcohols. The reaction is represented by the equation

$$R{\cdot}CO{\cdot}OEt + 4H \longrightarrow R{\cdot}CH_2{\cdot}OH + EtOH$$

This method was developed by Bouveault and Blanc (*Compt. rend.*, 1903, **136**, 1676; **137**, 60; *Bull. Soc. chim.*, 1904, [iii], **31**, 669). They found that though it could not be used for formic esters, it usually failed when the carboxyl is attached directly to the aromatic nucleus, and that the esters of α-hydroxy-acids were not reduced regularly, yet it gave good yields with the esters of the fatty acids. Thus tetradecyl alcohol results from the reduction of ethyl myristate, methyl caprylate gives octyl alcohol, pelargonic ester yields nonyl alcohol. The esters of dibasic aliphatic acids are also reduced to glycols; suberic ester yielding decane ακ-diol, αα-dimethylsuccinic ester yields ββ-dimethyl-αδ-diol.

The process used by Bouveault and Blanc consists in adding a solution of the ester in 3—4 times its weight of alcohol to approximately 6 atomic proportions of sodium. A vigorous reaction takes place, and after it has subsided, the reduction is completed by heating under reflux till as much as possible of the sodium has reacted. Although excellent yields are often obtained by this method, the isolation of the alcohol sometimes presents serious experimental difficulties. Moreover, the yields may sometimes fall short of those expected owing, in some measure at least, to the hydrolysing action of the ethoxide on the unreduced ester. In the reduction of esters of campholic acid, this form of loss has been reduced by using the difficultly hydrolysable phenyl and naphthyl esters instead of the less resistant ethyl and methyl esters (Rupe and Läuger, *Helv. Chim. Acta*, 1920, **3**, 272). It seems not unlikely that a similar procedure may be successful with many other acids.

Another method of avoiding loss of product is due to Prins (*Rec. trav. chim.*, 1923, **42**, 1050). His method consists in covering a saturated aqueous solution of sodium acetate with the ester to be reduced. The whole is cooled to − 5° and small pieces of sodium are added at intervals, followed by sufficient 30% acetic acid to maintain a neutral or faintly acid reaction to litmus. The yield of alcohol from fatty esters by this method is stated to reach 90% of the theoretical. Fatty aromatic esters give lower yields. The reduction requires about 3—5 days for completion.

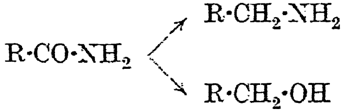
The use of toluene or light petroleum solutions of the ester has also been recommended (Ford and Marvel, *Organic Syntheses*, 1930, **10**, 62; Levene and Allen, *J. Biol. Chem.*, 1916, **27**, 443; Bleyberg and Ulrich, *Ber.*, 1931, **64**, 2504). The following description illustrates this modification of Bouveault and Blanc's method.

Preparation of Octadecanol from Ethyl Stearate.—23·5 G. of sodium are pressed into 20 g. of ethyl stearate diluted with 200 c.c. of light petroleum (b. p. 70—80°) and the mixture is heated on a water-bath under a reflux closed by a guard tube containing calcium chloride. Butyl alcohol (120 c.c.) is added—10 c.c. at a time—over a period of about 2 hours. The initial evolution of hydrogen is brisk, but it gradually slackens and the mixture thickens owing to the separation of sodium butoxide. When the greater part of the sodium has reacted, 95% alcohol (about 250 c.c.) is added till a clear solution results, which is heated on a water-bath for about 1 hour. Water is then added slowly so that the resulting reaction is not too vigorous. The thick paste which is formed first gradually goes into solution with the addition of more water, and a layer of concentrated sodium hydroxide separates. This is siphoned off and the upper layer washed with hot water to remove soap and ethyl alcohol. The petroleum and butyl alcohol are removed by distillation in steam. The non-volatile residue is taken up in light petroleum and washed with aqueous alcohol to remove the last traces of soap. The petroleum solution is dried over anhydrous sodium sulphate, then evaporated and distilled in high vacuum. Octadecanol is collected at 195—205°/0·2 mm., m. p. 59—60°—yield 15 g. (Bleyberg and Ulrich, *loc. cit.*).

Recently, catalytic methods have been developed for the reduction of the esters of fatty acids to alcohols and are employed for the manufacture of the higher aliphatic alcohols. The ethyl esters of lauric, myristic, valeric, and some dibasic acids have been smoothly reduced to alcohols by hydrogen under high pressure in presence of " copper chromite " as catalyst (Adkins and Folkers, *J. Amer. Chem. Soc.*, 1931, **53**, 1095; 1932, **54**, 1145).

The reduction of the alkyl esters of the higher fatty acids and also of neutral fats by hydrogen at high pressures and temperatures has been described by Schrauth, Schlenck, and Stickdorn (*Ber.*, 1931, **64**, 1314). O. Schmidt (*ibid.*, p. 2051) gives conditions for the catalytic reduction of esters of the higher fatty acids at ordinary pressure.

Reduction of amides of fatty acids by sodium and alcohol leads to the formation of the corresponding alcohol, but the product also contains the amine produced according to the scheme



$$R{\cdot}CO{\cdot}NH_2 \begin{array}{l} \nearrow R{\cdot}CH_2{\cdot}NH_2 \\ \searrow R{\cdot}CH_2{\cdot}OH \end{array}$$

(Guerbet, *J. pharm. Chim.*, 1899, [vi], **10**, 160.)

The reduction is effected by adding a solution of the amide in three times its weight of ethyl alcohol to 6 atomic proportions of sodium. After the first violent reaction is over, the mixture is heated till all the sodium has dissolved. Water is added and the product distilled in steam. A mixture of the alcohol and amine passes over. The amine is removed by treatment with acid. The yield of alcohol from the amides of *n*-hexoic, *n*-nonoic, and phenylacetic acids is approximately 25—30% (Bouveault and Blanc, *Compt. rend.*, 1904, **138**, 148).

(7) *Nitriles.*

The group $R{\cdot}C{\vdots}N$ present in all nitriles is unsaturated. As a consequence it enters into reaction with a large variety of reagents. It can be reduced and hydrolysed, and made to combine additively with the Grignard reagent, with halogen hydrides, alcohols, etc.

(a) *Hydrolysis.*—The ultimate products of the hydrolysis of a $-CN$ group are a $-CO_2H$ group and ammonia, but it is generally possible to control the conditions so that amides result. The complete hydrolysis of alkyl cyanides can be accomplished by heating under reflux with aqueous or aqueous alcoholic alkali (E. Frankland and Kolbe, *Annalen*, 1848, **65**, 298). Aryl cyanides generally may be hydrolysed under similar conditions, but usually it is more convenient to heat them with diluted sulphuric acid (20, 30, or 70% concentration) or with 20% hydrochloric acid.

$$R{\cdot}CN + H_2O \qquad R{\cdot}CO{\cdot}NH_2 \qquad R{\cdot}CO_2H + NH_3$$

The importance of the hydrolysis of nitriles lies in the fact that it supplies a method for the introduction of the carboxyl group. The reaction is not restricted to the alkyl and aryl cyanides, for it has been used for the preparation of α-hydroxy-acids from α-hydroxycyanides and of α-keto-acids from acyl cyanides. For the latter type of preparation the prolonged action of hot aqueous acids is not desirable; and the hydrolysis is better effected by prolonged contact with fuming hydrochloric acid at room temperature. A short period of heating at 70—80° is sometimes necessary to complete the hydrolysis.

Preparation of n-*Valeric Acid from* n-*Butyl Cyanide.*—*n*-Butyl cyanide (30 g.) is heated under reflux with a solution of 40 g. of sodium hydroxide in 50 c.c. of water diluted with 130 c.c. of alcohol. After heating for about 24 hours the alcohol is removed by distillation, and the residue dissolved in a small bulk of water and rendered faintly acid to congo paper by the addition of moderately concentrated sulphuric acid (60% concentration). The reaction mixture is cooled and stirred during this operation. Valeric acid which separates is removed, and a further amount can be obtained by extraction of the aqueous layer with ether. The acid and the ether extractions are combined, dried over anhydrous sodium sulphate, and fractionated. *n*-Valeric acid is collected at 180—185° (Frankland and Kolbe, *loc. cit.*; Adams and Marvel, *J. Amer. Chem. Soc.*, 1920, **42**, 312).

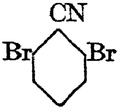
Preparation of Phenylacetic Acid from Benzyl Cyanide.—Benzyl cyanide (3 g.) is heated under a reflux with 10 c.c. of 70% sulphuric acid, till the mixture appears to boil. The hydrolysis then proceeds spontaneously without any further heating. Phenylacetic acid separates as a greyish crystalline mass on cooling. The mixture is cautiously diluted with water and collected by filtration. The acid is purified by solution in sodium carbonate, filtration from insoluble matter, and precipitation from the filtrate by the addition of a slight excess of dilute acid. After filtration and washing with a small amount of water, the product is crystallised from warm water, m. p. 76° (Städel, *Ber.*, 1886, **19**, 1951).

Preparation of Phenylacetamide from Benzyl Cyanide.—Benzyl cyanide (10 g.) is dissolved in concentrated sulphuric acid (40 g.). The solution is kept at room temperature overnight, and then poured into water. A precipitate results which is collected, pressed on a porous tile to free it from unchanged nitrile, and then stirred with cold dilute sodium carbonate solution to remove acid. It is finally washed with a small amount of cold water and then recrystallised from warm water—m. p. 155° (compare Maxwell, *Ber.*, 1879, **12**, 1764).

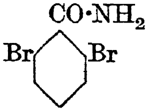
Preparation of Anisoylformic Acid ($CH_3O{\cdot}C_6H_4{\cdot}CO{\cdot}CO_2H$) *and its Amide from Anisoyl Cyanide.*—Fuming hydrochloric acid (20 c.c.) is added to anisoyl cyanide (5 g.) and the mixture kept in a sealed tube at room temperature for 10 days. It is then diluted with water and extracted with ether. The ethereal solution is shaken with potassium carbonate solution, dried over sodium sulphate, and evaporated. The residue is the amide of anisoylformic acid, m. p. 151—152°.

The addition of an excess of hydrochloric acid to the carbonate washings of the ethereal solution precipitates anisoylformic acid (Mauthner, *Ber.*, 1909, **42**, 188; compare Claisen and Moritz, *J.*, 1880, **37**, 692).

Some nitriles, particularly substituted benzonitriles with substituents in the *ortho* position with respect to the –CN group, are comparatively resistant to hydrolysis. Thus 2 : 6-dibromobenzonitrile (XXIX) yields only the corresponding amide (XXX) by the action of 80% sulphuric acid at 170°. Other nitriles which give the amide as the principal product of the action of moderately concentrated sulphuric acid at 180° are 2 : 4 : 6-trichlorobenzonitrile (XXXI), 2 : 6-dinitro-*p*-tolunitrile (XXXII), 6-nitro-4-bromo-*o*-tolunitrile (XXXIII) (Claus, *Annalen*, 1891, **266**, 224, 377; 1892, **269**, 212; Sudborough, *J.*, 1895, **67**, 602).



(XXIX.)



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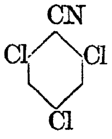
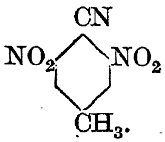
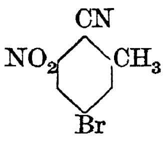


(XXXI.)



(XXXII.)



(XXXIII.)

Some of these nitriles have been hydrolysed to the corresponding acid by heating in sealed tubes with concentrated hydrochloric acid at 240°. A more convenient method of converting them into carboxylic acids consists in hydrolysing them to the amide by the action of moderately concentrated sulphuric acid and subsequently treating the latter with nitrous acid (Bouveault, *Bull. Soc. chim.*, 1892, [iii], **9**, 368). The following modification of Bouveault's process is due to Sudborough (*loc. cit.*).

The purified nitrile is heated with 25—30 times its weight of 90% sulphuric acid at 120—130° in an oil-bath. The conversion to amide is complete after about 1 hour. The mixture is then cooled, and the theoretical amount of nitrite in a small amount of water is introduced below the surface of the acid. The temperature is kept between 20° and 30° and the mixture stirred. It is finally heated gently in a capacious flask till the evolution of gas ceases, when it is poured into water. The precipitated acid is collected by filtration and purified by solution in sodium carbonate. From this solution the acid is precipitated by the addition of an excess of dilute mineral acid.

(b) *Alcoholysis.*—When nitriles are heated with alcoholic sulphuric acid or hydrochloric acid, an ester is formed (Backunts and R. Otto, *Ber.*, 1876, **9**, 1590). Concentrated sulphuric acid is apparently more suitable for this purpose than hydrochloric acid (Spiegel, *Ber.*, 1918, **51**, 296).

$$R{\cdot}CN + EtOH + H_2O \longrightarrow R{\cdot}CO_2Et + NH_3$$

The general conditions for converting a nitrile directly into an ester consist in heating the nitrile with an equimolecular proportion of concentrated sulphuric acid and about 10 molecular proportions of ethyl alcohol under reflux at 130—135° or in sealed tubes at 130—140°. It should be noted, however, that aromatic nitriles with substituents in the *ortho* position resist esterification by this method (Spiegel, *loc. cit.*; Pfeiffer and Matton, *Ber.*, 1911, **44**, 1115).

Preparation of Phenylacetic Ester.—A mixture of 22 g. of benzyl cyanide, 12 g. of concentrated sulphuric acid, and 30 g. of absolute alcohol is heated under reflux in an oil-bath at 100—130° for 3 hours. The excess of alcohol is then distilled off and the residue mixed with about 150 c.c. of water. The ester, which separates as an oil, is taken up in ether, the ethereal solution dried and then fractionated, b. p. 229°—yield about 20 g.

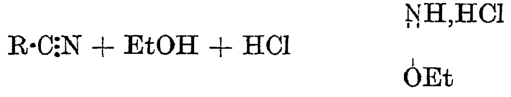
(c) *Reduction.*—Nitriles in general are reduced smoothly to primary amines by the action of sodium on alcoholic solutions of the nitriles (Ladenburg, *Ber.*, 1885, **18**, 2956; 1886, **19**, 780).

$$R{\cdot}C{:}N + 4H \qquad R{\cdot}CH_2NH_2$$

Preparation of Phenylethylamine.—A solution of 50 c.c. of benzyl cyanide in 350 c.c. of absolute alcohol contained in a ¾-litre flask is heated to boiling on a sand-bath. Sodium (40 g.) is then added through the condenser during 15 minutes and the solution heated till all the sodium has dissolved (about 1 hour). While the product is still warm, 150 c.c. of water are added and the alcohol is distilled off from a water-bath. The aqueous alkaline residue is then distilled in steam and the distillate (about 3 litres) acidified by the addition of 9 c.c. of concentrated sulphuric acid and evaporated to dryness on a water-bath—yield of sulphate 39 g. (Wohl and Berthold, *Ber.*, 1910, **43**, 2183).

The aliphatic nitriles are also reduced by means of zinc and acid, but the yields are unsatisfactory. The usual methods of hydrogenation by the Sabatier–Senderens method (*Compt. rend.*, 1905, **140**, 482) or in alcoholic solution using palladium or platinum as catalysts (Paal and Gerum, *Ber.*, 1909, **42**, 1553) give serious amounts of secondary amine as well as the normal product of reduction. Rosenmund and Pfankuch (*Ber.*, 1923, **56**, 2258) have described conditions for catalytic reduction of some nitriles to primary amines using acetic acid as a solvent.

(d) *Formation of Imino-ethers.*—In the complete absence of moisture, nitriles react with alcohols in the presence of hydrogen chloride to form the hydrochlorides of imino ethers :



$$\mathrm{R{\cdot}C{:}N + EtOH + HCl} \qquad \begin{array}{l}\mathrm{NH,HCl}\\ \vdots\\ |\\ \mathrm{OEt}\end{array}$$

(Pinner, *Ber.*, 1883, **16**, 352, 1643; 1890, **23**, 2917; Glock, *ibid.*, 1888, **21**, 2650; Eitner and Wetz, *ibid.*, 1893, **26**, 2840). The general method of preparations is illustrated by the following descriptions.

Preparation of Acetimino Ethyl Ether Hydrochloride.—Perfectly dry acetonitrile (100 g.) (dried by keeping in contact with calcium chloride for 1 week and then fractionating) is mixed with 113 g. of dry ethyl alcohol. Dry hydrogen chloride is passed in till the weight has increased by 92 g. During the passage of the hydrogen chloride the mixture is surrounded by a bath of ice and salt. Acetimino ether hydrochloride separates out on keeping for 2 or 3 days. Moisture must be excluded (Dox, *Organic Syntheses*, 1928, **8**, 1).

Preparation of Benzimino Ethyl Ether Hydrochloride.—A mixture of equimolecular proportions of benzonitrile and absolute alcohol is cooled by an external bath of ice and salt and saturated with dry hydrogen chloride. The liquid is kept for several days, moisture being excluded, and then evaporated under reduced pressure. The residue solidifies to a crystalline mass of the hydrochloride on keeping. It is obtained as transparent prisms, m. p. 118—120° (Pinner, *Ber.*, 1883, **16**, 1654).

Most nitriles yield imino-ethers by the above procedure, exceptions being aromatic nitriles with substituents in the *ortho* position with respect to the –CN group (Pinner, *Ber.*, 1890, 23, 2917). Some aliphatic nitriles containing two or more chloro- or bromo-groups in the α-position, such as dichloro-, trichloro-, tribromo-, and dichloronitro-acetonitriles, do not form imino-ethers by the general method, nor does nitroacetonitrile. Chloro-, bromo-, or iodo-acetonitriles, however, react normally to form imino-ethers (Steinkopf and Malinowski, *Ber.*, 1911, **44**, 2898).

(e) *Reaction with Phenols. Hoesch Synthesis of Phenolic Ketones.*—Imines are formed when equimolecular proportions of suitable phenols and nitriles in ethereal solution are saturated with hydrogen chloride in presence of anhydrous zinc chloride. Hydrolysis of the imine results in the formation of phenolic ketones (Hoesch, *Ber.*, 1915, **48**, 1122; 1917, **50**, 462). (See p. 99.)

(f) *Conversion of Nitriles into Aldehydes.*—This depends on the formation of an imino-chloride from the nitrile by the action of hydrogen chloride, and its subsequent reduction to an aldimine. This, by hydrolysis, gives an aldehyde (H. Stephen, *J.*, 1925, **127**, 1874).

$$R{\cdot}C\vdots N \xrightarrow{HCl} R{\cdot}CCl\colon NH \xrightarrow{H_2} R{\cdot}CH\colon NH \xrightarrow{H_2O} R{\cdot}CHO + NH_3$$

This method has been applied successfully to aliphatic and aromatic nitriles, and the yields are generally good, although *o*-tolunitrile and α-naphthonitrile give unsatisfactory results (Stephen, *loc. cit.*). The process fails with 4-cyanodiphenyl (Shoppee, *J.*, 1933, 39).

Stephen gives the following general directions:

Finely-powdered anhydrous stannous chloride (1½ mol. proportions) is suspended in dry ether which is saturated with dry hydrogen chloride till the mixture separates into two layers. The nitrile (1 mol.) is now added with vigorous shaking. After a few minutes a white crystalline aldimine stannichloride, $(R{\cdot}CH\colon NH,HCl)_2SnCl_4$, begins to separate. It is collected by filtration and hydrolysed by warming with water. The aldehyde is either steam distilled or taken up in ether.

(g) *Reaction with Grignard Reagent.*—The addition of an ethereal solution of a nitrile to an ethereal solution of a Grignard reagent generally results in the formation of a compound of the type $RRC\colon N{\cdot}MgCl$, the reaction usually being completed by warming on a water-bath. In the aromatic series, the free ketimine $RRC\colon NH$ may be isolated by decomposition of the initial additive compound with ice-cold ammonium chloride solution. The preparation of mixed aliphatic aromatic ketimines by this method requires special precautions (Moureu and Mignonac, *Compt. rend.*, 1913, **156**, 1801). The reaction of the Grignard reagent with nitrile is generally used for the preparation of ketones. This is achieved by treatment of the ketimine magnesium chloride with dilute acid.

$$RRC\colon NMgCl + 2HCl + H_2O \longrightarrow RRCO + MgCl_2 + NH_4Cl$$

It is noteworthy that acetonitrile reacts with methyl or ethyl magnesium bromide in an abnormal manner, for none of the expected ketone is formed. Instead, some of the Grignard reagent is decomposed to give paraffin hydrocarbons, and a number of nitrogenous compounds more complex than acetonitrile are formed. Benzyl cyanide behaves somewhat similarly, although a small yield of the required ketone is obtained. The homologues of acetonitrile react more normally to furnish ketones as the principal product, but even here a number of by-products are formed.

The tendency for acetonitrile and benzyl cyanide and to a less extent other nitriles to react in the imino-form seems to be responsible for the production of undesirable by-products in these reactions (Bruylants, *Bull. Acad. roy. Belg.*, 1922, [v], **8**, 7; Baerts, *Bull. Soc. chim. Belg.*, 1922, **31**, 184; Rondou, *ibid.*, p. 231).

TABLE XII.

Carboxylic Acids.

	B. p.	M. p.	Methyl ester. B. p.	Ethyl ester. B. p.	*p*-Nitrobenzyl ester. M. p.	*p*-Bromophenyl acyl ester. M. p.	Amide. M. p.	Anilide. M. p.	Chloride. B. p.	
Formic	100°	8°	32°	54°	31°	—	3°	47°	—	Reduces $HgCl_2$ and acidified $KMnO_4$; CO with conc. H_2SO_4; *p*-toluidide, m. p. 53°.
Acetic	118	16	57	77	78	85°	82	115	55°	*p*-Toluidide, m. p. 147°.
Propionic	140	—	79	98	31	59	79	105	80	*p*-Toluidide, m. p. 124°.
Acrylic	140	—	85	101	—	—	84	104	—	
Propiolic	144 dec.	—	—	—	—	—	—	—	—	B. p. 85°/50 mm.; reduces warm aq. $AgNO_3$; ammoniacal CuCl ⟶ green ⟶ brown amorphous precipitate.
*iso*Butyric	155	—	92	110	oil	77	129	105	92	*p*-Toluidide, m. p. 104°.
n-Butyric	163	—	102	120	35	63	114	90	100	*p*-Toluidide, m. p. 72°.
Pivalic	163	35	101	118	—	—	—	154	105	
Pyruvic	165	13	135	155	—	—	—	—	—	Phenylhydrazone, m. p. 178°; *p*-nitrophenylhydrazone, m. p. 219°.
*iso*Crotonic	169	—	—	—	—	—	—	—	—	
*iso*Valeric	176	—	116	134	—	68	135	115	115	*p*-Toluidide, m. p. 98°.
n-Valeric	186	—	127	145	—	63	104	60	127	*p*-Toluidide, m. p. 70°.
n-Caproic	205	—	150	166	—	71	98	95	152	
n-Heptylic	223	—	173	189	—	—	94	71	175	
Lactic	syrup		145	154	oil	112	—	—	—	Ca salt sol. in 9 parts water at 15°; Zn salt in 59 parts water at 8°; Fenton's reagent ⟶ pyruvic acid.
α-Phenylpropionic	265	—	221	230	—	—	92	—	—	
Oleic	—	14	—	—	—	62	72	—	—	
Lævulic	—	33	191	202	61	84	—	—	—	Phenylhydrazone, m. p. 108°; *p*-nitrophenylhydrazone, m. p. 174°.
β-Phenylpropionic	280	48	236	247	36	—	105	92	114/ 14 mm.	
Bromoacetic	208	50	144	159	89	—	91	130	—	
Thioglycollic	103/ 13 mm.	—	—	—	—	—	—	—	—	Dithioglycollic acid, m. p. 108°.
Elaidic	119/ 16 mm.	51	—	—	—	—	92	—	—	
Myristic	—	53	296	306	—	—	102	84	168/ 15 mm.	
Trichloroacetic	—	55	—	—	—	—	141	94	—	
Palmitic	—	62	[30]	[24]	43	81	106	90	—	
Phenylthioglycollic	—	62	—	—	—	—	—	—	—	Sulphone, m. p. 112°.
Chloroacetic	185	63	130	144	—	—	119	134	—	
Stearic	—	69	[38]	[33]	—	78	108	93	—	
Phenylacetic	—	76	220	227	65	89	154	117	—	
Glycollic	—	79	150	160	—	138	—	—	—	Free acid usually obtained as syrup; Ca salt sol. in 80 parts water at 17·7°; Zn and Pb salts not readily sol.

TABLE XII—*continued.*

Carboxylic Acids.

	B. p.	M. p.	Methyl ester. B. p.	Ethyl ester. B. p.	*p*-Nitrobenzyl ester. M. p.	*p*-Bromophenyl acyl ester. M. p.	Amide. M. p.	Anilide. M. p.	Chloride. B. p.	
p-Toluic	—	177	33	235	105	153	159	140	225	
Anisic	—	183	[45]	269	132	152	—	—	—	
2 : 4-Dinitrobenzoic	—	183	[70]	[41]	142	—	203	—	[42—46]	
β-Naphthoic	—	183	[77]	310	—	—	192	170	[43]	
Succinic	—	185	[19]	216	88	211	242	226	—	Succinanilic acid, m. p. 145° → succinanil, m. p. 153°; succinic anhydride, m. p. 120°; succinimide, m. p. 126°.
Camphoric	—	187	—	—	66	—	192	—	—	Camphoranilic acid, m. p. 203° → anil, m. p. 116°; camphoric anhydride, m. p. 216°.
Aconitic	—	191	—	—	155	—	—	—	—	
Phthalic	—	195	282	298	155	—	265	250	—	Phthalanilic acid, m. p. 166° → phthalanil, m. p. 205°; phthalic anhydride, m. p. 128°; phthalimide, m. p. 223°.
Protocatechuic	—	194 d.	—	—	—	—	—	—	—	FeCl₃ → blue-green.
2-Chloro-3 : 5-dinitrobenzoic	—	199	[87]	[54]	—	—	—	—	—	
Coumaric	—	200 d.	—	—	152	—	—	—	—	
m-Hydroxybenzoic	—	200	[70]	[73]	106	—	—	—	—	$FeCl_3$, no coloration.
3 : 5-Dinitrobenzoic	—	207	107	—	—	—	183	234	—	
Vanillic	—	207	[62]	[44]	140	—	—	—	—	$FeCl_3$, no coloration.
p-Hydroxybenzoic	—	213	[131]	[116]	198	—	—	—	—	$FeCl_3$, no coloration.
Phenylthioglycollic-*o*-carboxylic	—	213	—	—	—	—	—	—	—	
3-Nitrophthalic	—	218	[69]	—	189	—	—	—	—	Anhydride, m. p. 163°.
Tannic	—	200—220	—	—	—	—	—	—	—	$FeCl_3$ → deep blue; alkaline soln. → brown. Ppts. gelatine; yields pyrogallol on heating.
2-Hydroxy-3-naphthoic	—	222	[75]	—	—	—	—	—	—	$FeCl_3$ → blue.
Diphenic	—	229	—	—	—	—	—	—	—	Anhydride, m. p. 217°.
5-Nitrosalicylic	—	230	[48]	—	—	—	225	224	—	$FeCl_3$ → blood red.
p-Chlorobenzoic	—	236	[43]	238	129	—	179	194	—	
o-Nitrocinnamic	—	237	[72]	—	132	—	185	—	—	
p-Nitrobenzoic	—	241	[96]	—	168	—	201	204	—	
Tetrachlorophthalic	—	250	[92]	[60]	180	—	—	—	—	Anhydride, m. p. 252°.
p-Bromobenzoic	—	250	[81]	—	139	—	189	197	—	
Gallic	—	263	—	—	—	—	—	—	—	$FeCl_3$ → blue-black ppt.
p-Nitrocinnamic	—	285	—	—	168	—	—	—	—	
Fumaric	—	†	[102]	218	150	—	—	—	—	
Terephthalic	—	‡	[140]	[44]	263	—	—	—	—	
Naphthalic	—	—	—	—	—	—	—	—	—	Anhydride, m. p. 266°; sol. *in* H_2SO_4 → blue fluorescence.

The reaction of alkyl cyanides with aryl magnesium halides appears to be more satisfactory.

Preparation of Phenyl Alkyl Ketones from Alkyl Cyanides.—The following directions are given by Shriner and Turner (*J. Amer. Chem. Soc.*, 1930, **52**, 1268), and have been applied successfully to the preparation of the *n*-alkyl aryl ketones from methyl to amyl. The best yields are obtained when 4 mol. proportions of the Grignard reagent are used.

The aryl magnesium bromide is prepared from 25 g. of magnesium and 160 g. of bromobenzene in dry ether.

The nitrile (0·25 g.-mols.) diluted with 100 c.c. of ether is added to the Grignard reagent during 15 minutes, the solution being stirred during the addition. After keeping overnight, it is poured on a mixture of 500 g. of ice and 300 c.c. of concentrated hydrochloric acid. The aqueous layer is separated and refluxed vigorously for 1 hour. It is then cooled and extracted with ether. The ketone in the ether extract is obtained by fractional distillation.

Preparation of ω-Methoxyacetophenone.—An ethereal solution of methoxyacetonitrile (10·4 g.) (Polstroff and Meyer, *Ber.*, 1912, **45**, 1911) is gradually added to a cooled solution of phenylmagnesium bromide, from 22·9 g. of bromobenzene and 3·5 g. of magnesium in 150 c.c. of ether. The additive compound thus formed is kept overnight and then decomposed by adding ice-water and cold dilute sulphuric acid. The ethereal layer is separated, washed with sodium carbonate solution and water, then dried and distilled under reduced pressure, b. p. 118—120°/15 mm. (Pratt and Robinson, *J.*, 1923, **123**, 748).

(h) *Other Reactions.*—Some nitriles are converted into amides by the action of dilute hydrogen peroxide solution in feebly alkaline solution (Radziszewski, *Ber.*, 1885, **18**, 355). As far as this reaction has been examined, it appears to be satisfactory with aromatic nitriles except those with *ortho*-substituents. Alkyl cyanides, in general, do not give satisfactory results (Deinert, *J. pr. Chem.*, 1895, [ii], **52**, 431).

The addition of hydrogen sulphide to nitriles results in the formation of thioamides

$$\mathrm{Ph{\cdot}CN + H_2S \longrightarrow Ph{\cdot}CS{\cdot}NH_2}$$

Preparation of Thiobenzamide.—A mixture of benzonitrile (20 g.), alcoholic ammonia (60 c.c.), and alcohol (60 c.c.) is saturated with hydrogen sulphide and then heated on a water-bath in a closed vessel for 1 hour. The alcohol and ammonia are driven off by distillation and the residue of thiobenzamide is crystallised from hot water, m. p. 116°—yield almost theoretical (Gabriel and Heymann, *Ber.*, 1890, **23**, 158).

Nitriles can also combine additively with hydroxylamine (Tiemann, *Ber.*, 1884, **17**, 128; Tiemann and Krüger, *ibid.*, p. 1685; Nordmann, *ibid.*, p. 2746; Jacoby, *ibid.*, 1886, **19**, 1500; Eitner and Wetz, *ibid.*, 1893, **26**, 2844).

The addition of aniline to some nitriles with the formation of amidines has been recorded (v. Walther and Grossmann, *J. pr. Chem.*, 1908, [ii], **78**, 476).

CHAPTER VII

AMINES

- (1) General Reactions.
  - (a) Salt Formation.
  - (b) Acylation and Alkylation.
    - 1. Acylation.
    - 2. Formation of Substituted Ureas.
    - 3. Alkylation of Primary and Secondary Amines.
    - 4. Arylation of Primary and Secondary Amines.
    - 5. Formation of Quaternary Ammonium Salts.
  - (c) Degradation of Amines.
  - (d) Oxidation of Amines.
  - (e) Action of Nitrous Acid.
    - 1. Primary Amines.
      - (a) Aliphatic Amines.
      - (b) Esters of α-Amino-Acids.
      - (c) Aromatic Amines.
    - 2. Secondary Amines.
    - 3. Tertiary Amines.
  - (f) Replacement of the Amino Group by Hydroxyl.
  - (g) Action of Nitric Acid.
  - (h) Action of Halogens.
  - (i) Action of Sulphuric Acid.
- (2) Special Reactions of Diamines.
  - (a) 1 : 2-Diamines.
  - (b) 1 : 3-Diamines.
  - (c) 1 : 4-Aromatic Diamines.
  - (d) Formation of Cyclic Compounds from Aliphatic Diamines.
- (3) Quaternary Ammonium Compounds.

(1) *General Reactions.*

(a) *Salt Formation.*

THE formulation of amines as substituted ammonias allows of three types: primary—general formula $R{\cdot}NH_2$; secondary—general formula $RR'NH$; tertiary—general formula $RR'R''N$. The groups replacing the hydrogens of ammonia may be alkyl, aryl, or their substituted derivatives; unsaturated radicles; heterocyclic residues; or the nitrogen may be a part of a heterocyclic group as in pyridine.

The nature of the groups attached to nitrogen has a pronounced influence on the basic properties of the resulting amine. In general, the alkylamines are strongly basic, distinctly alkaline to litmus, and in the moist state combine with carbon dioxide. Indeed, the lower alkylamines are more strongly basic than ammonia, and can be titrated accurately with acids using methyl-orange or bromophenol blue as indicator. The presence of an aryl group reduces the basicity so that aniline and its homologues, although forming salts with dilute mineral acids, have no appreciable effect on litmus and do not abstract carbon dioxide from the air, nor can they be estimated satisfactorily by titration with acids in presence of the usual indicators; indeed, their hydrochlorides behave as free acids on titration with standard aqueous alkali using phenolphthalein. The effect on the basicity is still more marked if more than one aryl group is present. Thus diphenylamine yields salts which are extensively hydrolysed in water with the partial separation of the free base. Triphenylamine behaves as a neutral compound and forms no salts. However, an additive compound with perchloric acid must be excepted.

The following table gives the ionisation constants (× 10^7) at 18° of the lower alkylamines (Moore and Winmill, *J.*, 1912, **101**, 1671).*

NH_3	0·294	$C_2H_5NH_2$	6·73
CH_3NH_2	4·87	$(C_2H_5)_2NH$	10·59
$(CH_3)_2NH$	14·21	$(C_2H_5)_3N$	7·87
$(CH_3)_3N$	0·72	$n\text{-}C_3H_7NH_2$	4·68
		$(n\text{-}C_3H_7)_2NH$	9·16

The following table gives the affinity constants of some of the aromatic bases (Farmer and Warth, *J.*, 1904, **85**, 1713; compare Arnall, *ibid.*, 1920, **117**, 837).

Aniline	$5{\cdot}3 \times 10^{-10}$	*o*-Nitraniline	$5{\cdot}6 \times 10^{-1}$
o-Toluidine	$7{\cdot}3 \times 10^{-11}$	*m*-Nitraniline	$4{\cdot}0 \times 10^{-1}$
m-Toluidine	$2{\cdot}9 \times 10^{-10}$	*p*-Nitraniline	$1{\cdot}2 \times 10^{-1}$
p-Toluidine	$1{\cdot}1 \times 10^{-9}$	*p*-Chloraniline	$1{\cdot}5 \times 10^{-1}$
a-Naphthylamine	$9{\cdot}9 \times 10^{-11}$	*p*-Bromaniline	$1{\cdot}0 \times 10^{-1}$
β-Naphthylamine	$2{\cdot}0 \times 10^{-10}$		

Although the introduction of one nitro-group into the nucleus of aniline reduces the basicity so markedly, the nitranilines are still basic enough to yield salts with mineral acids, although such salts are extensively hydrolysed by water. The presence of more than one nitro in the nucleus has the effect of reducing the basicity still further, so that the resulting amines have little tendency to salt formation. The same remark applies to the introduction of a halogen group.

In its simplest form, the preparation of salts of amines consists in adding a slight excess of the appropriate acid to the amine. Such acids are dilute sulphuric acid, concentrated or dilute hydrochloric or hydrobromic acids. If there is no separation of the salt, the resulting solution may be evaporated on a water-bath or in a vacuum desiccator till crystallisation takes place. When the crystallisation of halogen hydride salts from aqueous media is unsatisfactory, they may be obtained by passing the dry halogen hydride into a solution of the amine in benzene, chloroform, or ether. This method is particularly convenient for the preparation of the halogen hydride salts of the alkylanilines and dialkylanilines and of the amines which yield salts which are extensively hydrolysed by water. Thus the hydrochlorides of the dialkylanilines are readily obtained in a crystalline state by saturating a solution of the amine in dry ether with dry hydrogen chloride. Moisture must be rigidly excluded (compare Reilly and Hickinbottom, *J.*, 1918, **113**, 103; 1920, **117**, 131). The hydrochlorides of the lower monoalkylanilines are best prepared in benzene solution, but this method is not so satisfactory with alkylanilines containing large alkyl groups.

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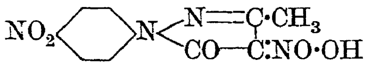
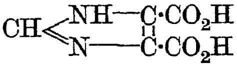
* It should be noted that E. A. Werner (*J.*, 1918, **113**, 900; 1919, **115**, 1010) considers that the relative strengths of the ethylamines are not accurately represented by the values in this table.

Most amines form well-crystalline salts with picric acid, which can be used to characterise the bases or to separate them from mixtures. These salts are usually prepared by mixing the components in a suitable solvent, the choice of which is determined by the relative solubilities of the picric acid, the salt, and the amine. Less rarely they can be obtained by double decomposition. Picrolonic acid (I) has also been used for the characterisation of amines, particularly when picric acid is unsatisfactory. It furnishes salts, which in general are more sparingly soluble than picrates and have higher melting points. The method has been employed principally for the characterisation of simple aliphatic hydroxylamines, morpholine bases, and some of the alkaloids (Knorr, *Annalen*, 1898, **301**, 5; 1899, **307**, 183; Knorr and Brownsden, *Ber.*, 1902, **35**, 4470; Matthes, *Annalen*, 1901, **315**, 109; Pictet and Gams, *Ber.*, 1909, **42**, 2952; Pictet and Spengler, *ibid.*, 1911, **44**, 2034). Iminazole dicarboxylic acid (II) has also been proposed for the characterisation of amines (Pauly and Ludwig, *Z. f. Physiol.*, 1922, **121**, 165).



(I.)



(II.)

Aromatic amines yield additive compounds with di- and tri-nitro-compounds such as 1 : 3 : 5-trinitrobenzene and 2 : 4 : 6-trinitrotoluene. The bodies are sometimes used for the characterisation of amines (see Pfeiffer, *Organische Molekülverbindungen*, 1922, pp. 226—236 and 239—242). Perchloric acid (70% aqueous solution) gives well-crystalline salts with some amines, and has been recommended for the purpose of separating and characterising such amines (K. A. Hofmann, Roth, Höbold, and Metzler, *Ber.*, 1910, **43**, 2624).

(b) *Acylation and Alkylation.*

The absence of a replaceable hydrogen attached to the nitrogen of tertiary amines distinguishes them in their reactions towards acylating and alkylating reagents. Thus primary and secondary amines, in general, yield substituted amides on acylation, while tertiary amines can be recovered unchanged after such treatment by adding water and aqueous alkali. The hydrogen of the amino-group in primary and secondary amines can also be replaced, under suitable conditions, by alkyl or aryl groups, or by $-CO{\cdot}NH_2$, $-Cl$, $-Br$, or $-NO_2$

groups. These reactions are considered in outline in the sections immediately following.

1. *Acylation.* The methods available may be classified broadly as follows: (*a*) heating with the appropriate acid, (*b*) reaction of the amine with the acid chloride, bromide, or anhydride; (*c*) less rarely reaction with the ester or even the amide.

The first of these methods is an extension of the process described in Chap. V for the preparation of amides, and consists simply in heating the appropriate amine with an excess of a suitable carboxylic acid.

$$\mathrm{R{\cdot}NH_2 + HO{\cdot}CO{\cdot}R' \longrightarrow R{\cdot}NH{\cdot}CO{\cdot}R' + H_2O}$$

The type of preparation is similar to that of acetamide.

Preparation of Acetanilide.—A mixture of 40 g. of aniline and 50 g. of glacial acetic acid is heated in a round-bottomed flask fitted with a long "rod and disk" fractionating column so that the temperature at the top of the column never exceeds 105°. In this way, the water which is formed in the reaction is continuously distilled away. The reaction is complete after several hours, when the contents of the flask are poured into about 300 c.c. of cold water. The acetanilide is collected by filtration, washed with a little water, and crystallised from hot water containing a small amount of alcohol, m. p. 114°.

The higher homologues of acetanilide are prepared similarly. Indeed, this process is frequently used for the characterisation of monobasic acids (see p. 197). It is noteworthy that the ease with which formic acid yields substituted formamides by this method far exceeds that of its homologues. Thus formanilide is obtained quite readily by warming aqueous 50% formic acid and aniline.

Thioacetic acid has been recommended for the preparation of acetyl derivatives, and it is stated to have the advantage that acetylation of aniline and its homologues proceeds in the cold; hydrogen sulphide is evolved (Pawlewski, *Ber.*, 1898, **31**, 661; 1902, **35**, 110).

$$\mathrm{CH_3{\cdot}CO{\cdot}SH + Ph{\cdot}NH_2 \longrightarrow Ph{\cdot}NH{\cdot}CO{\cdot}CH_3 + H_2S}$$

It is usually more convenient, as a general method of preparation, to use either the acid chloride or anhydride. Acid chlorides react with amines to form acyl derivatives and the hydrochloride of the amine

$$\mathrm{R{\cdot}CO{\cdot}Cl + 2R'{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NHR' + R'{\cdot}NH_2{,}HCl}$$

The separation of the hydrochloride from the acyl derivative depends naturally on the relative solubilities of the two compounds. The reaction can be effected in a solvent in which the amine hydrochloride is insoluble, or if the acyl derivative is insoluble in water, it is usually sufficient to extract the hydrochloride with water after the reaction.

Preparation of ω-Benzylsulphonyl Piperidide.—1 Mol. proportion of benzylsulphonyl chloride is added to 2 mol. proportions of piperidine in benzene solution. The precipitate of piperidine hydrochloride which separates is collected and the filtrate evaporated. Crystallisation of the residue from aqueous alcohol yields the pure sulphonyl derivative, m. p. 131°. Benzyl sulphonyl derivatives of other amines such as allylamine, dibutylamine, toluidine, etc. have been prepared similarly (Marvel and Gillespie, *J. Amer. Chem. Soc.*, 1926, **48**, 2943).

Preparation of Benzoyl-p-toluidine.—Benzoyl chloride (0·2 g.) is warmed gently with about twice its weight of *p*-toluidine in a water-bath till all reaction ceases. The product is then extracted with hot water containing some dilute hydrochloric acid till it is free from amine hydrochloride. The residue is crystallised from alcohol, m. p. 157°.

This method is a general one for the preparation of benzoyl- and arylsulphonyl derivatives of aromatic amines.

When the acyl chloride is comparatively stable to water and dilute and cold aqueous alkali, the introduction of the acyl group may be effected by the method due to Schotten (*Ber.*, 1888, **21**, 3430) and Baumann (*ibid.*, 1886, **19**, 3218). The amine suspended in dilute aqueous alkali (about 10% concentration) is treated with the suitable acyl chloride; about $1\frac{1}{4}$—$1\frac{1}{2}$ times the theoretical amount is usually sufficient. The mixture should be either stirred or shaken during the introduction of the acyl chloride and the shaking continued till most of the acyl chloride has reacted. The excess of acyl chloride is destroyed by heating the reaction mixture gently. The sparingly soluble acyl derivative, thus formed, is collected by filtration, washed with water until free from alkali, and purified by crystallisation from a suitable solvent. It is essential that the aqueous solution should remain alkaline throughout the acylation. This method succeeds with the chlorides of the aromatic acids, with chlorides of aromatic sulphonic acid, and with furoyl chloride. When the sulphonyl chlorides are used, the product from primary amines is soluble in alkali, while that from secondary amines is insoluble. This is the basis of a method of distinguishing and separating primary and secondary amines (Hinsberg and Kessler, *Ber.*, 1905, **38**, 906).

The Separation of Primary, Secondary, and Tertiary Amines by the Use of Benzenesulphonyl Chloride.—A mixture of the bases is suspended in 4 mol. proportions of 12% aqueous potassium hydroxide and then $1\frac{1}{2}$ mol. proportions of benzenesulphonyl chloride are added gradually while the mixture is shaken vigorously. When the reaction is complete the last traces of the sulphonyl chloride are removed by gently warming. The alkaline solution is then acidified with hydrochloric acid and the precipitated sulphonamides are collected by filtration or taken up in ether. Any tertiary amine present in the original mixture remains in the aqueous acid solution and can be recovered by making alkaline.

The sulphonamides may contain appreciable amounts of the disulphonyl derivative of the primary amine, and as it is insoluble in aqueous alkali, it is necessary to hydrolyse it to the monosulphonyl derivative. Accordingly, the collected sulphonamides are heated under reflux with an alcoholic solution of sodium ethoxide (0·8 g. of sodium in 20 c.c. of alcohol for every 1 g. of the original mixture of bases) for 15 minutes. The solution is then diluted with water, the alcohol distilled off, and the alcohol-free aqueous residue cooled. The benzenesulphonyl derivatives of the secondary amines are insoluble, and after collecting them either by solution in ether or by filtration, they are dried and weighed. The alkaline aqueous solution contains only the sulphonyl derivatives of the primary amines. They are precipitated by the addition of an excess of dilute mineral acid, collected, dried, and weighed.

When the primary amine present in the mixture of bases has a comparatively high molecular weight, the separation by the above method is generally uncertain owing to the sparing solubility of the alkali salt of the benzenesulphonyl derivative of the primary amine. It is then necessary to use the following method of separation, and Hinsberg recommends that it should be adopted with all amines containing more than seven carbon atoms.

The product, after treatment with sodium ethoxide, is evaporated and acidified. The precipitated mixture of sulphonamides is collected, dried, and then dissolved in dry ether in a flask fitted with a reflux condenser. Small pieces of sodium, or better sodium wire, are added, and the mixture is warmed gently under reflux for 6—8 hours. Some unchanged sodium should always be present at the end of this period. After cooling, the suspended matter is collected and washed with several small volumes of ether. The ethereal filtrate contains only the benzenesulphonyl derivative of the secondary amine. The residue, insoluble in ether, is a mixture of the sodium salt of the benzenesulphonyl derivatives of the primary amines and free sodium. It is evaporated with some alcohol, diluted with water, and then acidified.

Benzenesulphonyl chloride may be replaced by *p*-toluenesulphonyl chloride, but it is advisable in these circumstances to have a small volume of ether present to facilitate the reaction between the amines and the acid chloride.

When this method is used for the quantitative determination of primary, secondary, and tertiary amines in a mixture, approximately accurate results are obtained if proper precautions are observed. It is obvious, however, that it cannot be applied to those secondary and primary amines which do not react smoothly with toluene- or benzene-sulphonyl chlorides. Among such amines are alkylanilines containing *tert.*-alkyl groups attached to nitrogen, triphenylamine, and some nitranilines (compare Hickinbottom, *J.*, 1933, 946).

Naphthalene- and anthraquinone-sulphonyl chlorides have also been used for the detection of primary and secondary amines (Hinsberg, *Ber.*, 1900, **33**, 3527).

Other methods of acylation involve the action of the acid chloride on an ethereal solution of the amine containing suspended potassium carbonate (Claisen, *Ber.*, 1894, **27**, 3182); acylation in pyridine solution.

Preparation of Benzanilide.—A solution of aniline (18 g.) in 180 c.c. of dry ether is heated under reflux after adding 42 g. of finely-powdered potassium carbonate. Benzoyl chloride (28 g.) is then slowly added and the heating continued for several hours. The ether is finally distilled off, water added, and the benzanilide collected by filtration—yield 24 g., m. p. 163° (Claisen, *loc. cit.*).

Acetylation of the primary aromatic amines is most conveniently effected on a small scale by the use of acetic anhydride. The reaction between acetic anhydride and aniline and its homologues proceeds very readily, and is best brought about by adding the anhydride to a suspension of the amine in about 5 volumes of water. Heat is generated in the reaction, and the suspension rapidly becomes pasty owing to the separation of the acetyl derivative. When the amine has a comparatively high molecular weight, it is usually more convenient to suspend the base in aqueous acetic acid before adding the anhydride. The use of alcohol as a diluent for the acetylation of amines with acetic anhydride in the cold has the advantage that the excess of anhydride can be removed simply by one or two evaporations with alcohol (Lumière a Barbier, *Bull. Soc. chim.*, 1906, [iii], **35**, 625). Acetylation w aqueous or alcoholic acetic anhydride is not satisfactory with primary arylamines containing negative substituents in the nucleus.

The method of acetylation, just indicated, has the advantage that there is no tendency to the formation of diacetyl derivatives, which is the case when undiluted acetic anhydride is used. Thus when aniline (10 g.) is heated with four times its weight of acetic anhydride for 1 hour the product is a mixture from which 10 g. of diacetylaniline and 5·6 g. of acetanilide may be isolated (Sudborough, *J.*, 1901, **79**, 534). The presence of substituents such as $-CH_3$, $-NO_2$, $-Cl$, $-Br$ in the *ortho* position to the amino-group appears to favour the formation of diacetyl derivatives. Thus an excellent yield of diacetyl-*o*-toluidine results when *o*-toluidine is heated under reflux with four times its weight of acetic anhydride.

The presence of nitro-groups and to a less extent bromo- and chloro-groups in the nucleus of aromatic amines retards acetylation at room temperature. The effect becomes more pronounced with the accumulation of negative groups. Thus a solution of 2 : 4 : 6-tribromaniline in an excess of acetic anhydride may be kept at room temperature for a fortnight without the formation of any acetyl compound. The presence of a small quantity of concentrated sulphuric acid catalyses the acetylation very markedly. Thus the addition of two drops of concentrated sulphuric acid to a solution of 1 g. of 2 : 4 : 6-tribromaniline in 20 g. of acetic anhydride yields pure 2 : 4 : 6-tribromacetanilide after keeping for 10 minutes at room temperature. The product is isolated by pouring into water (A. E. Smith and Orton, *J.*, 1908, **93**, 1242; Orton, *ibid.*, 1902, **81**, 495).

The most convenient method for the isolation of the acetyl derivatives of the lower alkylanilines consists in distilling a mixture of equal volumes of the amine and acetic anhydride. After rejecting the fractions below 200°, the approximately pure acetyl derivative is collected. Many of these acetyl compounds crystallise on cooling (Hickinbottom, *J.*, 1930, 994).

It is obvious that the structure of tertiary amines does not permit of the formation of amides by reaction with acyl chlorides or anhydrides. Numerous observations have been made, however, which indicate that tertiary amines are able to combine additively with acid chlorides to yield compounds which, in general, are decomposed by water with the regeneration of the original amine. Thus pyridine and acetyl chloride combine in the ratio of 1 : 1, and the resulting compound furnishes pyridine hydrochloride and ethyl acetate by treatment with alcohol (Dennstedt and Zimmermann, *Ber.*, 1886, **19**, 75; Freudenberg and Peters, *ibid.*, 1919, **52**, 1463). Oxalyl chloride also combines with pyridine (Jones and Tasker, *P.*, 1908, **24**, 271; Freudenberg and Peters, *loc. cit.*). Dehn (*J. Amer. Chem. Soc.*, 1912, **34**, 1399) and Dehn and Ball (*ibid.*, 1914, **36**, 2091) describe additive compounds of benzoyl and acetyl chloride with triethylamine, pyridine, dimethylaniline, and some other tertiary amines. Vorländer and Nolte (*Ber.*, 1913, **46**, 3212) have described additive compounds of trimethylamine with arylsulphonyl chlorides which are sufficiently stable to water to yield platinichlorides and aurichlorides.

(2) *Formation of Substituted Ureas.*—The salts of primary and secondary amines with cyanic acid isomerise more or less readily to furnish substituted ureas (Wurtz, *Compt. rend.*, 1851, **32**, 414).

$$R\cdot NH_2,HCNO \longrightarrow R\cdot NH\cdot CO\cdot NH_2$$

The reaction thus resembles the conversion of ammonium cyanate to carbamide. The following descriptions illustrate its application.

Preparation of Methylurea.—An aqueous solution of methylamine sulphate is evaporated on a water-bath with the calculated amount of potassium cyanate. The dry residue is extracted with hot absolute alcohol. Evaporation of the alcoholic extract yields methylurea, which may be purified by precipitating it as nitrate by the addition of nitric acid.

After crystallisation of the nitrate from water, it is decomposed by treatment with an excess of an aqueous suspension of barium carbonate. The mixture is evaporated and then extracted with hot absolute alcohol. Pure methylurea is obtained by evaporation of the alcoholic extract, m. p. 101—102° (Wurtz, *loc. cit.*).

aa-Dimethylurea, ethylurea, *iso*butyl- and *sec*-butyl-ureas have been prepared by a similar process, but with these, purification through the nitrate is not advisable (Leuckart, *J. pr. Chem.*, 1880, [ii], **21**, 29; Dixon, *J.*, 1895, **67**, 559).

Preparation of Phenylurea.—A solution of aniline hydrochloride in water is treated with the calculated amount of potassium cyanate dissolved in water. After keeping for some hours the solution has set to a crystalline mass. It is drained under suction, washed with cold water, and recrystallised from boiling water, m. p. 147° (Weith, *Ber.*, 1876, **9**, 820; A. W. Hofmann, *Annalen*, 1849, **70**, 131).

Homologues of aniline similarly yield arylureas.

The use of acetic acid as a solvent is an alternative procedure.

Preparation of o*-Tolylurea.*—A solution of 21·4 g. of *o*-toluidine in 20 c.c. of acetic acid is diluted with 400 c.c. of water and then mixed with a solution of 16 g. of potassium cyanate in 40 c.c. of water. An abundant precipitate of *o*-tolylurea is obtained. It is purified by crystallisation from alcohol, m. p. 190—191° (Walther and Wlodkowski, *J. pr. Chem.*, 1899, [ii], **59**, 273).

Preparation of β-Naphthylurea.—The necessary amount of powdered potassium cyanate is added to a solution of β-naphthylamine in glacial acetic acid. The resulting mixture is warmed till the cyanate has dissolved, and the solution poured into a large volume of water. β-Naphthylurea is precipitated, m. p. 213—214°.

Primary and secondary amines react smoothly with *iso*cyanic esters to furnish substituted ureas. Phenyl *iso*cyanate is generally used for this purpose, and the reaction is effected by warming equimolecular amounts of the amine and the *iso*cyanate in a suitable non-hydroxylic solvent; light petroleum is very convenient for this purpose.

$$Ph\cdot NCO + R\cdot NH_2 \longrightarrow Ph\cdot NH\cdot CO\cdot NHR$$

It is of the utmost importance that moisture be excluded from the reaction by using only carefully dried solvents and amine, since phenyl *iso*cyanate reacts with water to give diphenylurea. The use of α-naphthyl *iso*cyanate has the advantage over phenyl *iso*cyanate in that it is less sensitive to water, and consequently there is less risk of the formation of undesirable by-products (Neuberg and Manasse, *Ber.*, 1905, **38**, 2359; French and Wirtel, *J. Amer. Chem. Soc.*, 1926, **48**, 1736).

Phenyl *iso*thiocyanate reacts similarly with amines to yield the corresponding thioureas. The reaction is brought about in a manner quite similar to that of phenyl *iso*cyanate.

(3) *Alkylation of Primary and Secondary Amines.*—The progressive substitution of the hydrogens of a primary amine leads to the successive formation of a secondary and a tertiary amine. When the substituting group is alkyl, this can be achieved conveniently by reaction of the amine with the appropriate alkyl halide or alkyl sulphate. The composition of the final product depends largely on the proportions of the reactants employed and also on the experimental conditions. In general it is difficult to restrict the substitution to the exclusive formation of any one type of amine, and the product usually consists of a mixture of both types of amine with important amounts of unchanged amine and frequently some quaternary ammonium salt. The formation of such a mixture, when alkyl halides are used, is obviously due to the liberation, in the reaction, of halogen hydride, which then combines with the amines present. The distribution of the halogen hydride is dependent on the relative strengths of the amines, on their relative proportions, and also on the solubilities of the amine salts in the reaction mixture. In the alkylation of arylamines, the solid which separates usually contains a high proportion of the salt of the amine which is being alkylated, leaving in solution a relatively large amount of the alkylated amine to react further with the alkyl halide. These difficulties can be overcome, at least to some extent, by effecting the alkylation in the presence of some reagent which will combine with the liberated halogen hydride such as alkali carbonate or bicarbonate.

*Preparation of Dimethyl-*p*-xylidine.*—A mixture of 10 g. of *p*-xylidine, 30 g. of methyl iodide, 25 g. of sodium carbonate, and 250 c.c. of water is heated under reflux for 6 hours. The oil is separated, dried in contact with anhydrous potassium carbonate after diluting with ether, and then distilled, b. p. 205°.

*Preparation of Dimethyl-*o*-toluidine.*—*o*-Toluidine (10 g.) is heated with 75 g. of methyl iodide under reflux in a water-bath at 50° for ½ hour. The excess of methyl iodide is distilled off, the residue dissolved in water and treated with an excess of aqueous potash. The amine thus liberated is taken up in ether, dried in contact with potassium hydroxide, and the solvent evaporated. The residual amine is subjected to a further treatment with methyl iodide in order to complete the conversion into tertiary amine. The amine is finally purified through its picrate. The purified amine distils at 185°.

Preparation of Ethyl-β-naphthylamine.—β-Naphthylamine (20 g.), ethyl iodide (33 g.), and a solution of 40 g. of sodium carbonate in 500 c.c. of water are heated together under reflux for 3 hours. The oily amine is then taken up in ether, the ethereal solution dried over potash, and the ethyl-β-naphthyl-[illegible]

powdered β-naph [illegible]
is heated in closed vessels at 120° for 7—8 hours with 85 g. of ethyl iodide.

The oil resulting from the reaction is dried in contact with solid caustic soda and then fractionated. Diethyl-β-naphthylamine is collected at 310—312°/764 mm. (Morgan, *J.*, 1900, **77**, 823).

*Preparation of Dimethyl-*o*-bromaniline.*—This amine is obtained by heating a mixture of 17 g. of *o*-bromaniline, 37 g. of sodium carbonate, 430 c.c. of water, and 50 g. of methyl iodide under reflux for 20 hours. The crude product is driven over by a current of steam and removed from the distillate by ether. After removing the solvent the residual mixture of amines is mixed with acetic anhydride to convert the secondary and any primary amines into acetyl derivatives. After keeping for a few hours the mixture is distilled in steam and then sodium carbonate added. The pure tertiary amine passes over and is separated from the distillate by means of ether. After the usual operations of washing and drying it is distilled under reduced pressure. Pure dimethyl *o*-bromaniline is collected at 107—108°/14 mm. (Auwers, *Ber.*, 1907, **40**, 2530, *footnote*).

Preparation of Ethyl-α-naphthylamine.—A solution of 85 g. of ethyl bromide in 80 c.c. of alcohol is added to a boiling solution of 100 g. of α-naphthylamine in 240 c.c. of alcohol. A crystalline precipitate of ethyl-α-naphthylamine hydrobromide is slowly produced. When the reaction is complete, the precipitate is collected and treated with an excess of aqueous potash. The ethyl-α-naphthylamine thus liberated distils at 191°/16 mm. as a colourless oil which darkens on exposure to air (Morgan and Micklethwait, *J.*, 1907, **91**, 1516).

The above methods can be employed for the preparation of secondary amines, but it is usually necessary, except in special circumstances, to isolate the secondary amine through its nitrosamine; reduction of the nitrosamine with tin and hydrochloric acid or fission by the action of hot acids (see p. 327) yields the pure secondary amine. This can be avoided and the yield of secondary amine materially increased by taking advantage of the fact that the metal derivatives of many substituted amides of the type R·CO·NHR react with alkyl halides. The product of the alkylation yields the required secondary amine on hydrolysis.

$$\mathrm{R{\cdot}CO{\cdot}NHR'} \longrightarrow \mathrm{R{\cdot}CO{\cdot}NR'Na} \xrightarrow{\mathrm{R''I}} \mathrm{R{\cdot}CO{\cdot}NR'R''} \longrightarrow \mathrm{R{\cdot}CO_2H} + \mathrm{NHR'R''}$$

For this purpose acetanilide and its homologues are suitable, while the formyl derivatives of primary arylamines have also been used. Arylsulphonyl derivatives of primary amines have also been employed for this purpose.

Preparation of Methylaniline.—A solution of 100 g. of acetanilide in 600 c.c. of xylene (dried in contact with sodium) is treated with 25 g. of sodium wire and then heated for 2 or 3 hours in an oil-bath at 130°. Hydrogen is evolved and the acetanilide is converted into the sodium salt—a dazzling white spongy mass which appears to fill the whole vessel. After cooling, somewhat more than the necessary amount of methyl iodide (calculated on the sodium) is added. The reaction proceeds spontaneously and is completed by warming gently. The greater part of the xylene is then distilled off and the residue boiled for 8—12 hours with alcoholic potash. The alcohol is then removed by distillation, the residue acidified, and the remainder of the xylene distilled off in steam. The solution remaining in the flask is then rendered alkaline and distilled in steam. Methylaniline passes over and is recovered from the distillate by ether. After the usual operations of drying and removal of the solvent the residue is distilled. Methylaniline is collected at 190—192° (P. Hepp., *Ber.*, 1877, **10**, 328).

The following general conditions are given by Pictet and Crépieux (*Ber.*, 1888, **21**, 1107) for the use of formanilide in the preparation of secondary amines.

A mixture of equimolecular proportions of formanilide and the alkyl bromide is treated with one molecular proportion of alcoholic potash. A vigorous reaction often sets in at room temperature and is completed by warming. When complete, the alcoholic solution is filtered from suspended potassium salt and the alcohol distilled off. The residual formyl derivative is then distilled. Hydrolysis by means of acid or alkali yields the required secondary amine.

Preparation of Dimethylethylenediamine.—Ethylenedibenzenesulphonamide (100 g.), prepared from benzenesulphonamide and ethylene dibromide (Hinsberg and Strupler, *Annalen*, 1895, **287**, 222), is heated under reflux with a slight excess of aqueous alkali, 90 g. of methyl iodide, and 50 g. of alcohol. After about 1 hour the alcohol is distilled off, the residue warmed with dilute alkali, and washed with water. Dibenzenesulphonyl derivative of dimethylethylenediamine remains as a white crystalline, crumbly mass. It separates from hot water as white needles, m. p. 131°.

It is hydrolysed by heating with concentrated hydrochloric acid in sealed tubes at 160°. The acid solution resulting from this treatment is evaporated to dryness and then distilled with alkali. The base passes over at 119°, and is an oily liquid which readily abstracts carbon dioxide from the air (Schneider, *Ber.*, 1895, **28**, 3074).

Preparation of Methyl-β-naphthylamine.—The benzenesulphonyl derivative of β-naphthylamine is dissolved in the calculated amount of *N*-caustic soda and shaken with somewhat more than the theoretical amount of dimethyl sulphate. β-Naphthylmethylbenzenesulphonamide separates out in almost theoretical yield, m.p. 107°.

It is hydrolysed by heating 120 g. of the sulphonamide in 100 c.c. of acetic acid with 275 c.c. of concentrated hydrochloric acid for 5—6 hours in an autoclave at 150—160°. The resulting solution is boiled with decolorising charcoal, filtered, and then made alkaline with caustic soda. The oil which separates is taken up in ether, the ethereal solution dried and distilled. Methyl-β-naphthylamine is collected as a viscous oil, b. p. 165—170°/12 mm.—yield about 70% of theory (Pschorr and Karo, *Ber.*, 1906, **39**, 3140).

*Preparation of Methyl-*m*-nitraniline.*—*p*-Toluenesulphonyl *m*-nitraniline (22 g.) dissolved in 100 c.c. of alcohol containing 7 g. of sodium hydroxide is heated under reflux and 20 g. of methyl iodide are added gradually. After 13 hours, the alcohol is distilled off and the residue extracted with dilute aqueous sodium hydroxide to remove unchanged toluene sulphonyl derivative. The insoluble material is collected by filtration, washed with water, and then crystallised from alcohol. The pure *p*-toluenesulphonyl derivative of *m*-nitromethylaniline is thus obtained, m. p. 114°. It is hydrolysed to methyl-*m*-nitraniline by heating with 70% sulphuric acid (Morgan and Micklethwait, *J.*, 1912, **101**, 145).

Another method of preparing homologues of methylaniline consists in heating the appropriate alkyl halide with a large excess of the arylamine, and removing the excess remaining after the reaction by precipitation with aqueous zinc chloride. This process has been applied to the preparation of a number of alkylanilines with quite satisfactory results (Hickinbottom, *J.*, 1930, 992). It has also been applied to the preparation of alkylanilines with tertiary alkyl groups (Hickinbottom, *J.*, 1933, 946).

Preparation of n-*Propylaniline.*—Aniline (230 g.; 2½ mols.) is heated with *n*-propyl bromide (1 mol.) under reflux in a boiling water-bath for 6 hours. The product is rendered alkaline, the amines are separated and treated with a solution of 150 g. of zinc chloride in 150 c.c. of water. The mixture, when cooled and stirred, is rapidly converted into a thick paste which, after 12 hours, is drained on a large Buchner funnel, washed with cold water, and pressed to remove as much of the water as possible. It is then extracted several times under reflux with boiling light petroleum. The extracts are combined with the petroleum extract of the aqueous washings of the zinc chloride, washed with water, and dried in contact with solid potassium carbonate. Removal of the solvent leaves crude *n*-propylaniline, which after two fractionations is obtained almost pure, b. p. 218—222°—yield 94 g.; 70% of theory. A further quantity (10 g.) is collected between 222° and 230°, and contains appreciable amounts of dipropylaniline.

If necessary, the main fraction may be further purified by crystallisation of the hydrochloride from benzene or through its acetyl derivative.

In the preparation of higher alkyl anilines (from amyl upwards) some of the excess of aniline may be removed by careful fractionation, and the remainder by treatment with zinc chloride.

The alkylation of amines can be also effected by the use of dialkyl sulphates. This procedure, however, is generally confined to the use of the commercially available dimethyl sulphate. Alkylation using these reagents can be brought about either in a indifferent solvent or in presence of aqueous alkali (Ullmann and Wenner, *Ber.*, 1900, 33, 2476). It is more usual to employ aqueous alkali in conjunction with dimethyl sulphate. The dialkyl sulphates may be replaced by aryl sulphonyl esters (Ullmann and Wenner, *Annalen*, 1903, **327**, 120; Földi, *Ber.*, 1922, **55**, 1535; Ferns and Lapworth, *J.*, 1912, **101**, 281).

Preparation of Dimethylaniline.—Methylaniline (53 g.) and the methyl ester of *p*-toluenesulphonic acid (93 g.) are heated together in acetone (100 c.c.). Trimethylphenylammonium-*p*-toluenesulphonate separates out in brilliant hygroscopic scales, m. p. 159°—yield 40 g.

The mother-liquor from the filtration of the quaternary ammonium salt is evaporated and then made alkaline. Dimethylaniline separates, and is isolated by steam distillation—yield 40 g. (Földi, *loc. cit.*).

On an industrial scale, use is made of the fact that the alcohols react with the salts of primary amines at about 200° to furnish mono- and di-alkylarylamines. Thus in the industrial preparation of methylaniline, a mixture of aniline hydrochloride (55 parts) and methyl alcohol (16 parts) is heated at 180°. For the preparation of dimethylaniline, aniline and methyl alcohol are mixed in the proportion of 80 : 78, 8 parts of sulphuric acid added, and then heated in an autoclave at 235°. On a smaller scale, the sulphuric or hydrochloric acid may be replaced by other catalysts such as iodine. Mixtures of copper powder and sodium bromide or of copper halides and sodium halides are even more efficient catalysts (Hill and Donleavy, *J. Ind. Eng. Chem.*, 1921, **13**, 504; T. B. Johnson, Hill, and Donleavy, *ibid.*, 1920, **12**, 636).

The preparation of secondary amines can be effected by reducing azomethines.

$$R{\cdot}CH{:}NR + 2H \longrightarrow R{\cdot}CH_2{\cdot}NHR$$

The reduction can be achieved electrolytically (Law, *J.*, 1912, **101**, 154); with zinc dust and aqueous alkali (Morgan, E.P. 102,834); with sodium and alcohol or with formic acid (Wallach, Hüttner, and Altenburg, *Annalen*, 1905, **343**, 54; Ishizaka, *Ber.*, 1914, **47**, 2456).

Another interesting method consists in treating an azomethine with a suitable alkyl iodide. When the addition of the alkyl halide is complete, the addition of water or alcohol liberates the required secondary amine and the aldehyde (Decker and Becker, *Annalen*, 1913, **395**, 362; Hamilton and Robinson, *J.*, 1916, **109**, 1033).

$$R{\cdot}CH{:}NR' + R''I \longrightarrow R{\cdot}CH{:}NR'R''I \xrightarrow{H_2O} R{\cdot}CHO + R'R''NH,HI$$

(4) *Arylation of Primary and Secondary Amines.*—The introduction of an aryl group is usually accompanied with some difficulty owing to the stability of the halogen of the aryl group. Thus chloro- and bromo-benzene do not react with aniline under conditions comparable with those employed for the preparation of ethylaniline. The reaction, however, is facilitated by the presence of copper bronze or of cuprous iodide (Goldberg, *Ber.*, 1906, **39**, 1691; 1907, **40**, 4541; D.R.-P. 185,663: 187,870).

Preparation of o-*Nitrodiphenylamine.*—*o*-Nitraniline (3 g.), finely powdered potassium carbonate (1 g.), bromobenzene (12 c.c.), and a trace of cuprous iodide are heated together over a bare flame for 12 hours. The excess of bromobenzene is then removed by steam distillation, leaving a reddish oil, which, after treatment with warm hydrochloric acid to dissolve unchanged nitraniline, solidifies. The *o*-nitrodiphenylamine thus obtained is collected by filtration and crystallised from alcohol. It separates from this solvent as orange platelets, m. p. 75° (Goldberg, *Ber.*, 1907, **40**, 4545).

Preparation of Diphenylamine.—Acetanilide (10 g.), finely-powdered potassium carbonate (5 g.), bromobenzene (20 g.), and some cuprous iodide are heated together in boiling nitrobenzene for 15 hours. The solvent and excess of bromobenzene are removed by steam distillation. A dark oil remains in the flask. It is taken up in ether, filtered, dried, and the solvent evaporated. Crude acetyldiphenylamine is thus obtained, m. p. 102° after crystallisation from alcohol.

It is hydrolysed by heating it under reflux with a mixture of 30 c.c. of concentrated hydrochloric acid and 30 c.c. of alcohol for 3 hours. The alcohol is then distilled off and the diphenylamine isolated by steam distillation of the remaining solution—yield 7·5 g. (Goldberg, *loc. cit.*, p. 4543).

Preparation of Phenylanthranilic acid.—Anthranilic acid (2 g.), bromobenzene (3·2 g.), potassium carbonate (2 g.), and about 0·1 g. of copper bronze are heated together in 12 c.c. of boiling nitrobenzene for 3 hours. After removing the solvent by steam distillation the residue is acidified. Phenylanthranilic acid separates—yield 3 g. It is purified by crystallisation from benzene, m. p. 181° (Goldberg, *Ber.*, 1906, **39**, 1691).

In contrast to the behaviour of bromo- and chloro-benzenes, 2 : 4-dinitrochlorobenzene and the corresponding bromo-compound react readily with primary and secondary amines without the aid of a catalyst. The products thus formed are generally crystalline, and are used for the characterisation and identification of primary and secondary amines.

Preparation of 2 : 4-Dinitrodiphenylamine.—Equimolecular proportions of aniline and 2 : 4-dinitrochlorobenzene are warmed together in a water-bath for a few minutes. On cooling, dinitrodiphenylamine is obtained as a bright red crystalline mass, m. p. 155—156° after crystallisation from alcohol.

Other primary aromatic amines, such as the homologues of aniline, aminophenols, and diamines, behave similarly. The reaction may conveniently be carried out in alcoholic solution or in the presence of sodium acetate (Willgerodt, *Ber.*, 1876, **9**, 977; Nietzki and Ernst, *ibid.*, 1890, **23**, 1852; Reitzenstein, *J. pr. Chem.*, 1903, [ii], **68**, 251; Meigen, *ibid.*, 1908, [ii], **77**, 472; Schöpff, *Ber.*, 1889, **22**, 900).

Preparation of 2 : 4-*Dinitropropylaniline.*—A slight excess of an alcoholic solution of propylamine is added to an alcoholic solution of 2 : 4-dinitrobromobenzene and the mixture warmed in a water-bath. On cooling or on adding water, dinitropropylaniline separates as yellow needles, m. p. 95°.

Other aliphatic amines react similarly (Romburgh, *Rec. trav. chim.*, 1885, **4**, 189).

(5) *Reaction of Tertiary Amines with Alkyl Halides: Formation of Quaternary Ammonium Salts.*—Tertiary amines combine additively with alkyl iodides to furnish quaternary ammonium salts. The general method of preparation is to mix the requisite components, sometimes diluted with a suitable solvent. The combination may take place at room temperature or it may be necessary to heat the mixture.

$$R'R''RN + RHal \qquad R''R'RRNHal.$$

The alkyl halide may be replaced by dialkyl sulphates or the alkyl esters of arylsulphonic acids, when the sulphate or the aryl sulphonate of the quaternary ammonium compound results.

Preparation of Methyl Tripropyl Ammonium Iodide.—Tripropylamine is mixed with somewhat more than the necessary amount of methyl iodide, with or without the addition of dry ether. Combination is rapid, and the quaternary ammonium salt which is thus formed is purified by crystallisation from alcohol ether. It is obtained as glistening platelets, m. p. 207—208° (Pope and Read, *J.*, 1912, **101**, 528).

Preparation of Methyl Ethyl Propyl iso*Butylammonium Iodide.*—A mixture of ethylpropyl*iso*butylamine with a slight excess of methyl iodide soon becomes turbid and deposits a yellow oil, which gradually changes to a white crystalline mass. It is kept in a desiccator till the reaction is complete. The resulting ammonium salt is purified by crystallisation from acetone—m. p. 195° (Pope and Read, *loc. cit.*, 523).

Preparation of Phenyl Dimethyl Allylammonium Iodide.—A mixture of dimethylaniline (48 g.) and allyl iodide (67 g.) is kept for some days, when the semi-solid mass which is formed is finely ground, filtered, and washed with a little acetone. It is purified by solution in absolute alcohol and precipitation with dry ether—m. p. 88—89° (Harvey, *J.*, 1904, **85**, 412).

The formation of quaternary ammonium salts has frequently been used for the characterisation of tertiary amines. For this purpose, methyl iodide has received the widest application. Recently, the methyl ester of *p*-toluenesulphonic acid has been recommended as a general reagent for this purpose (Marvel, Scott, and Amstutz, *J. Amer. Chem. Soc.*, 1929, **51**, 3638). The following general procedure is recommended for the preparation of the quaternary ammonium *p*-toluenesulphonates.

The amine (1 g.) is heated with 2—3 g. of methyl ester of *p*-toluenesulphonic acid in 10 c.c. of dry boiling benzene for ½ hour. After cooling, the salt is filtered off and purified by crystallisation from alcohol or ethyl acetate.

Not only do alkyl halides and esters of arylsulphonic acids react with tertiary amines to form quaternary ammonium salts, but iodoacetic esters can yield similar compounds with some amines;

benzyl piperidine, aliphatic tertiary amines, and quinoline appear to react most readily. ω-Bromoacetophenone has been shown in a few instances to behave similarly.

Preparation of Carbethoxymethyl Triethyl Ammonium Iodide.
$EtO_2C{\cdot}CH_2{\cdot}NEt_3{\cdot}I$.
—Triethylamine (4 g.) and iodoacetic ester (7·9 g.) are mixed at room temperature. After keeping for some time a transparent crystalline mass is formed which after several crystallisations from acetone furnishes pure carbethoxymethyl triethyl ammonium iodide—brilliant prisms, m. p. 138—139° (E. Wedekind, *Annalen*, 1901, **318**, 104).

The ease of formation of quaternary ammonium salts is dependent on the constitution of the reactants. This is illustrated by the following table, which gives the velocity constants for the reaction of allyl bromide with tertiary amines at 40°.

Dimethylaniline	1·08	Methylpropylaniline	0·48
Methylethylaniline	0·71	Pyridine	0·43
Diethylaniline	0·094	Quinoline	0·063
Benzylmethylaniline	0·123	*iso*Quinoline	0·485
Dimethyl-*o*-toluidine	0·057	2-Methylquinoline	0·035
Dimethyl-*m*-toluidine	1·54	Methyltetrahydroquinoline	0·413
Dimethyl-*p*-toluidine	2·80		

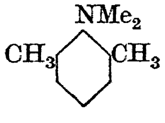
(E. R. Thomas, *J.*, 1913, **103**, 595; compare Menschutkin, *Ber.*, 1895, **28**, 1398; 1897, **30**, 2775, 2966; 1905, **38**, 2465; Wedekind, *Annalen*, 1901, **318**, 90; *Ber.*, 1899, **32**, 511.)

The following table gives the ratio of the velocity constants for the reaction of some alkyl iodides with dimethylaniline and tri*iso*amylamine at 40°.

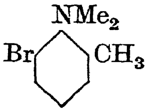
	Dimethylaniline.	Tri*iso*amylamine.
Allyl iodide	362	295
Methyl iodide	48	327
Ethyl iodide	3	4
n-Propyl iodide	1	1

(R. W. D. Preston and H. O. Jones, *J.*, 1912, **101**, 1931.)

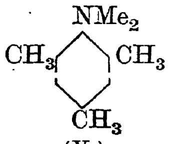
The retarding effect of substituents adjacent to the amino-group is seen from a comparison of the values for dimethyl-, *o*-, *m*-, and *p*-toluidines and for quinoline and *iso*quinoline. The effect is still more marked if there are two substituents in the *ortho* position. Thus the tertiary amines (III) and (IV) do not react with methyl iodide at 100°, although isomeric amines having other configurations form quaternary ammonium salts comparatively easily (E. Fischer and Windaus, *Ber.*, 1900, **33**, 1967).



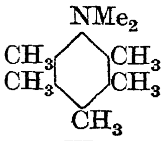
(III.)



(IV.)



(V.)



(VI.)

Dimethylmesidine (V) and dimethylaminopentamethylbenzene (VI) similarly do not yield quaternary ammonium salts (Hofmann, *Ber.*, 1885, **18**, 1824; 1872, **5**, 718).

(*c*) *Degradation of Amines.*

One of the early methods for carrying out this change consisted in heating the dry halogen hydride salt of an alkylamine. By selecting suitable conditions—depending largely on the substance under investigation—it is possible to split off one or more of the alkyls and to convert a tertiary amine successively into a secondary, a primary amine, and finally to ammonia (Hofmann, *Proc. Roy. Soc.*, 1860, **10**, 595). Thus trimethylamine hydrochloride heated at 285° yields dimethylamine hydrochloride, methyl chloride, and trimethylamine. At higher temperatures the product may contain methylamine or ammonium chloride, while methyl chloride is evolved (Vincent, *Compt. rend.*, 1877, **85**, 667; compare *ibid.*, 1877, **84**, 1139). This method does not appear to have received any notable application to the higher alkylamines. It has been applied more widely to the alkyl arylamines. Thus methylaniline, heated in a gentle stream of hydrogen chloride, yields aniline hydrochloride and methyl chloride. Tribenzylamine behaves similarly (Lauth, *Compt. rend.*, 1873, **76**, 1209; compare Städel, *Ber.*, 1886, **19**, 1947). Distillation of dimethylaniline hydrochloride yields methyl chloride, aniline hydrochloride, and methylaniline. It has recently been shown that the monoalkylaniline hydrobromides, from ethyl to *iso*amyl, decompose smoothly on heating at between 250° and 300° with the elimination of the alkyl group as a mixture of olefin and alkyl bromide. Under these conditions a relatively small amount of the alkyl group migrates to the nucleus with the formation of a *para*-substituted aminoalkylbenzene (Hickinbottom and Ryder, *J.*, 1931, 1281). If the heating is effected in closed vessels so that the products of the decomposition cannot escape, the yield of the *p*-aminoalkylbenzene is increased at the expense of volatile products. This constitutes the rearrangement first observed by Hofmann (*Ber.*, 1872, **5**, 704, 720; 1874, **7**, 526). Accounts of other conditions for effecting this rearrangement and a discussion of the nature of the reactions involved are to be found in the following papers: Reilly and Hickinbottom, *J.*, 1920, **117**, 103; Hickinbottom, *ibid.*, 1927, 64; Hickinbottom and Waine, *ibid.*, 1930, 1558; Hickinbottom and Preston, *ibid.*, p. 1566; Hickinbottom, *ibid.*, 1932, 2396; 1934, 1700.

Alkylanilines with tertiary alkyl groups lose the alkyl group comparatively readily; heating with aqueous mineral acids at 110—140° for several hours is usually sufficient to bring about an extensive elimination of the alkyl group (Hickinbottom, *J.*, 1933, 1070; compare *Nature*, 1933, **131**, 762).

An interesting application of the decomposition of amine salts is found in the preparation of olefins and particularly of dienes by heating the phosphate (Harries, *Ber.*, 1901, **34**, 300; *Annalen*, 1903, **328**, 322; Harries and Antoni, *ibid.*, p. 105; Harries and de Osa, *Ber.*, 1903, **36**, 2997; Harries and M. Johnson, *ibid.*, 1905, **38**, 1832). By this method γ-amino-α-phenylbutane furnishes a mixture of phenylbutenes; diaminomethylpentane yields methylpentadiene; 1 : 3-diamino*cyclo*hexane gives 1 : 3-*cyclo*hexadiene. The method has also been used for the preparation of some menthadienes.

Another type of degradation results in the formation of nitrosamines from tertiary amines by the action of tetranitromethane (Erich Schmidt and Heinrich Fischer, *Ber.*, 1920, **53**, 1537; Schmidt and Schumacher, *ibid.*, 1921, **54**, 1414).

$$(RCH_2)_3N + C(NO_2)_4 \longrightarrow (R{\cdot}CH_2)_2N{\cdot}NO + R{\cdot}CHO + CH(NO_2)_3$$

Dialkyl arylamines react best with the tetranitromethane in presence of pyridine; aliphatic amines in acetic acid solution. The following general procedure is recommended for the conversion of dialkyl arylamines.

Tetranitromethane (1·1 mol. proportions) is slowly added to a solution of 1 mol. proportion of the amine and 1·2—1·5 mol. proportions of pyridine in alcohol. After the addition of all the tetranitromethane, the solution is heated in a water-bath till the odour of tetranitromethane has disappeared. It is then mixed with water (100 c.c. for every 10 g. of amine), an equal volume of saturated salt solution added, and the mixture extracted with ether. The ethereal extracts are combined, washed with saturated salt solution, then with carbonate solution, and finally steam distilled. The nitrosamine is extracted from the distillate with ether, the ethereal solution dried, and the nitrosamine recovered by evaporation of the solvent. It may be purified by distillation under reduced pressure. By this method 10 g. of dimethylaniline yielded 7·2 g. of methylphenylnitrosamine. The process has been shown to be applicable to a number of halogen-substituted dialkyl anilines.

The following is recommended for the conversion of aliphatic tertiary amines to the nitrosamines of the corresponding secondary amines.

An alcoholic solution of 1 mol. proportion of the tertiary amine and 2 mol. proportions of acetic acid is heated in a sealed tube for 3 hours with 1·1 mol. proportions of tetranitromethane. Considerable pressure develops in the tube, and caution is required not only in opening it, but also in limiting the quantity of the mixture in the tube. When the reaction is complete, the contents of the tube are poured into a separating funnel containing caustic potash solution (20 c.c. of 33% potash solution diluted with 100 c.c. of water for every 10 g. of tertiary amine). After shaking the mixture and adding saturated salt solution it is extracted with ether. The ethereal extracts are combined, washed with water, and then shaken mechanically with dilute sulphuric acid (10 c.c. of 3*N*-sulphuric acid diluted to 60 c.c. with water). The ethereal solution is dried in contact with anhydrous sodium sulphate and the solvent evaporated.

By this procedure 7·2 g. of tripropylamine, 6·1 g. of acetic acid, and 10·8 g. of tetranitromethane in 50 c.c. of alcohol gave 6 g. of dipropylnitrosamine, b. p. 59—61°/1·5 mm.

Nitric acid has a similar action on dialkyl arylamines if the conditions are suitable. This reaction is dealt with more fully on p. 290.

A method of less general application depends on the action of hypochlorous acid or chlorine in aqueous solution on aliphatic tertiary amines or on cyclic amines such as tropidine (Willstätter and Iglauer, *Ber.*, 1900, **33**, 1636; Meisenheimer, *ibid.*, 1913, **46**, 1148).

According to Meisenheimer the reaction proceeds as follows:

$$R_3N \xrightarrow{Cl_2} R_3NCl_2 \longrightarrow R_2NCl + HCl + R'{\cdot}CHO$$

Cyanogen bromide has been found to be a useful reagent for the removal of one alkyl group from tertiary amines. The reaction proceeds according to the equation (v. Braun, *Ber.*, 1900, **33**, 1438, 2730; 1902, **35**, 1279; 1907, **40**, 3933):

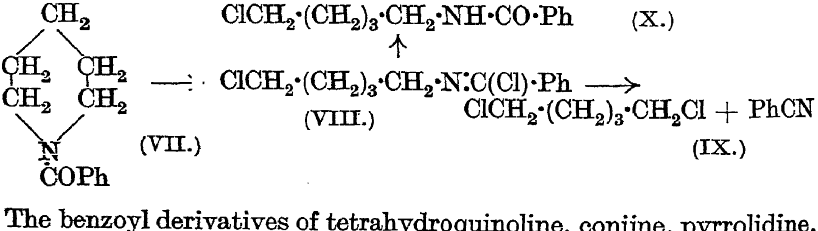
$$R'RN{\cdot}Alk + CNBr \qquad R'RN{\cdot}CN + AlkBr$$

Its application is illustrated by the following example:

Preparation of Methyl Cumidine from Dimethyl Cumidine.—Dimethyl cumidine (11·5 g.) is mixed with cyanogen bromide (7·5 g.) and shaken frequently at room temperature. The mass becomes fluid and assumes a yellow colour. After keeping at room temperature for some time, the methyl bromide and excess of cyanogen bromide are distilled off. Ether is added to the residue to precipitate the quaternary ammonium salt which has been formed by the action of the liberated methyl bromide on unchanged tertiary amine. The ethereal solution on fractionation yields the nitrile—b. p. 165°/10 mm.—yield 36% of theory. The cyanamide thus obtained is hydrolysed by heating with 30% sulphuric acid for 2—3 hours. The addition of an excess of aqueous alkali liberates ammonia and methyl cumidine, b. p. 111—112°/11 mm. (Sachs and Weigert, *Ber.*, 1907, **40**, 4356).

Tertiary amines derived from piperidine, tetrahydroquinoline, and dihydro*iso*indole may yield the normal cyanamide, or the ring may be opened (v. Braun, *Ber.*, 1900, **33**, 2734; 1907, **40**, 3914; 1909, **42**, 2035, 2219; 1910, **43**, 1353).

A more satisfactory method for opening the ring of such cyclic amines consists in heating the benzoyl derivatives with phosphorus pentachloride. Thus benzoylpiperidine (VII) yields successively (VIII), which can be hydrolysed to benzoylamino-ε-chloropentane (X), and dichloropentane (IX).



$ClCH_2{\cdot}(CH_2)_3{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}Ph$ (X.)

(VII.) $\longrightarrow$ $ClCH_2{\cdot}(CH_2)_3{\cdot}CH_2{\cdot}N{:}C(Cl){\cdot}Ph$ (VIII.) $\longrightarrow$ $ClCH_2{\cdot}(CH_2)_3{\cdot}CH_2Cl + PhCN$ (IX.)

The benzoyl derivatives of tetrahydroquinoline, coniine, pyrrolidine, and methyldihydroindole behave similarly (v. Braun, *Ber.*, 1904, **37**, 2812, 3210; 1905, **38**, 179; Braun and Steindorff, *ibid.*, 1904, **37**, 4581; Braun and Beschke, *ibid.*, 1906, **39**, 4119; Braun and Schmitz, *ibid.*, p. 4365).

Preparation of Benzoyl-ε-chloroamylamine.—A mixture of equimolecular proportions of benzoylpiperidine and phosphorus pentachloride is heated over a free flame in a round-bottomed flask fitted with a calcium chloride tube and a reflux condenser. When all the chloride has dissolved and the first vigorous reaction is over, the liquid is kept at boiling point for ¼ hour. It is then cooled, ice-water added, the greater part of the free acid neutralised, and finally distilled in steam. A small amount of benzonitrile and dichloropentane passes over. The non-volatile oil in the flask slowly solidifies. It is purified by draining on a tile and subsequently triturating with petroleum ether to remove some tarry matter. When dry it is distilled. Benzoyl-ε-chloroamylamine passes over at 230—240° as a yellow oil which solidifies. It separates from aqueous alcohol as a crystalline powder, m. p. 66° (Braun and Steindorff, *Ber.*, 1905, **38**, 2336).

Preparation of αε-Dichloropentane.—Equimolecular proportions of phosphorus pentachloride and benzoylpiperidine are heated together in an obliquely placed fractionating flask. When all the solid has dissolved, the flask is changed to its normal position and the mixture distilled. Considerable fractions are collected at 100—110° and 170—185°, while a black tarry residue remains in the flask. The distillate is poured on ice and the dichloropentane and benzonitrile formed in the reaction are driven over by distillation in steam. The distillate is extracted with ether, the solvent removed from the extract, and the residue heated with concentrated hydrochloric acid till all the benzonitrile is hydrolysed. Dichloropentane is isolated from the hydrolysis mixture by steam distillation and separated from the distillate by means of ether. The ethereal solution is washed with alkali and water, dried, and distilled. Pure αε-dichloropentane is collected at 79—80/21 mm.—yield 75—80% of theory.

An alternative method for the rupture of the ring of cyclic amines is described under the reactions of quaternary ammonium compounds.

(*d*) *Oxidation of Amines.*

By the oxidation of primary amines a large variety of products can be obtained, depending on the experimental conditions. From tertiary amines, however, the products are comparatively simple, nearly all of them yielding oxides by the action of neutral aqueous hydrogen peroxide.

$$R_3N + H_2O_2 \longrightarrow R_3N{:}O + H_2O$$

(Dunstan and Goulding, *J.*, 1899, **75**, 1004; Bamberger and Tschirner, *Ber.*, 1899, **32**, 342, 1882; Bamberger and Leyden, *ibid.*, 1901, **34**, 16).

Preparation of Trimethylamine Oxide.—An aqueous solution of trimethylamine (100 c.c. of 33% sol.) is mixed with 600 c.c. of pure hydrogen peroxide solution (3%). If the odour of the amine still persists after keeping for 24 hours at room temperature, a further amount of hydrogen peroxide solution (100—200 c.c.) should be added. When all the amine has been oxidised, the solution is evaporated under reduced pressure and the residue crystallised from ether-alcohol. The product is the hydrate of trimethylamine oxide, $(CH_3)_3N{:}O,2H_2O$. It forms long needles, m. p. 96°—yield up to 95%.

It is dehydrated by heating in an oil-bath at 120° under a pressure of 10—12 mm. and then slowly raising the temperature to 150°. When the water has been driven off, the temperature is raised to 180—200° The pure anhydrous amine oxide then sublimes on to the cooler parts of the flask. It is extremely hydroscopic (Dunstan and Goulding, *loc. cit.*; Meisenheimer, *Annalen*, 1915, **397**, 286).

Preparation of Methyl Ethyl Propylamine Oxide.—Methyl ethyl propylamine (10 g.) is shaken mechanically with 60 c.c. of 10% pure aqueous hydrogen peroxide, the stopper being loosened at intervals to liberate the free oxygen. The amine dissolves after several hours. The solution is then extracted several times with ether after placing platinum wire in it to decompose the excess of unchanged hydrogen peroxide. The aqueous solution is evaporated at 30—40° under reduced pressure. Treatment of the syrupy residue with a cold aqueous saturated solution of picric acid precipitates the picrate, which after crystallisation from water or from alcohol is obtained as dark yellow crystalline grains, m. p. 106—107° (Meisenheimer, *Annalen*, 1922, **428**, 260).

Preparation of Dimethylaniline Oxide.—Dimethylaniline (100 g.) and 2500 c.c. of 3% hydrogen peroxide solution (neutralised with magnesium carbonate) are stirred mechanically with a very efficient stirrer at 70—80° for 5 hours. The solution is evaporated to half its bulk over a free flame after filtering from suspended matter. The addition of a hot saturated aqueous solution of picric acid precipitates the picrate of dimethylaniline oxide, m. p. 137—138°—yield 295 g. (Bamberger and Tschirner, *loc. cit.*; Bamberger and Leyden, *loc. cit.*).

The formation of amine oxides from dialkyl arylamines appears to be hindered by the presence of an alkyl group in the *ortho* position with respect to the amino-group. When both *ortho* positions are occupied no amine oxide appears to be formed (Bamberger and Rudolf, *Ber.*, 1906, **39**, 4285).

Amine oxides can also be prepared by the use of benzoyl hydrogen peroxide or almost neutral Caro's acid (Meisenheimer, *Ber.*, 1919, **52**, 1671; Bamberger and Rudolf, *loc. cit.*). The action of ozone on a chloroform solution of some aliphatic tertiary amines also yields amine oxides (W. Strecker and Thienemann, *Ber.*, 1920, **53**, 2112; Strecker and Baltes, *ibid.*, 1921, **54**, 2701).

Dialkylarylamines with a free *para* position, such as dimethylaniline, yield other oxidation products under suitable conditions. With lead peroxide or potassium permanganate in sulphuric acid solution the free *para* positions unite with the formation of tetra-alkyldiamino-derivatives of diphenyl.

The oxidation of primary aromatic amines by means of Caro's acid converts the amino-group into a nitroso-group. In the aliphatic series this reaction is complicated by the fact that the oxidation products are in general more sensitive than the amines. Thus ethylamine by treatment with Caro's acid yields acetic acid as the principal product, with small amounts of nitroethane, acethydroxamic acid, acetoxime, and acetonitrile (Bamberger, *Ber.*, 1902, **35**, 4293; compare Bamberger and Seligmann, *ibid.*, p. 4299). The method is more satisfactory if the amino-group is attached to a tertiary carbon atom. Thus *tert.*-butylamine and *tert.*-amylamine yield successively the hydroxylamine and then the nitroso-compound (Bamberger and Seligmann, *Ber.*, 1903, **36**, 685). Aromatic amines are oxidised smoothly to the corresponding nitroso-compounds,

$$\mathrm{Ph{\cdot}NH_2 + 2O \longrightarrow Ph{\cdot}NO + H_2O.}$$

This reaction is an important one, in that it is a convenient method for the preparation of nitroso-derivatives of aromatic compounds. Furthermore, oxidation of the nitroso-compound thus formed yields a nitro-compound, and so the process has been used for the introduction of nitro-groups when the usual method of nitration is impracticable.

Preparation of 2 : 5-*Dinitrotoluene from* 5-*Nitro*-o-*toluidine*.—Finely-powdered ammonium persulphate (12 g.) is added gradually to 17 g. of ice-cold sulphuric acid, which is stirred mechanically. The mixture is poured on 70 g. of crushed ice, and then 2·5 g. of finely-powdered 5-nitro-*o*-toluidine are added. After keeping for 12 hours the mixture is diluted and the precipitate of 2-nitroso-5-nitrotoluene collected by filtration and washed with water.

Oxidation of the nitroso-group is effected by adding the moist substance, a little at a time, to an excess of fuming nitric acid heated on a water-bath. The heating is continued till the acid is no longer coloured. The mixture is then poured into water and the precipitated nitro-compound collected and crystallised from alcohol, m. p. 50—51°—yield of crude material, m. p. 48—49°, is 1·4 g. (Page and Heasman, *J.*, 1923, **123**, 3241).

Preparation of Nitrosomesitylene from Mesidine.—A solution of 37 g. of ammonium persulphate in 30 c.c. of concentrated sulphuric acid is poured on ice (500 g.) and the solution nearly neutralised by the addition of crystalline sodium carbonate (150 g.). While this solution is stirred mechanically, 10 g. of mesidine are added, sodium carbonate solution being also added at frequent intervals to keep the solution faintly alkaline. After 1½ hours, the brown solid produced by the oxidation is collected by filtration, washed with dilute hydrochloric acid, and triturated with light petroleum to free it from gummy matter. Nitrosomesitylene remains as a white crystalline mass, which, after crystallisation from alcohol, is obtained as colourless crystalline plates melting at 122—123°; a bluish liquid (Ingold and Piggott, *J.*, 1924, **125**, 173).

Preparation of 2-*Chloro*-3 : 6-*dinitrotoluene from* 6-*Chloro*-5-*nitro*-o-*toluidine*.—A solution of Caro's acid is prepared by adding 8·5 g. of powdered ammonium persulphate to 6·3 c.c. of concentrated sulphuric acid, and then pouring the solution after 1 hour on 17 g. of crushed ice. To this solution is added slowly 1·7 g. of 6-chloro-5-nitro-*o*-toluidine in 5·2 c.c. of concentrated sulphuric acid. A yellowish-grey solid commences to separate almost immediately. After 4 days an equal bulk of water is added and the solid nitroso-compound collected by filtration.

It is oxidised by adding it, small quantities at a time, to 12 c.c. of fuming nitric acid heated on a water-bath. When nitrous fumes cease to be evolved, the solution is diluted. The dinitrochlorotoluene separates as an oil which rapidly solidifies. It crystallises from light petroleum as colourless needles, m. p. 62—63° (Morgan and Glover, *J.*, 1924, **125**, 1599).

Other methods for the oxidation of the amino-group to nitroso- or nitro- include the use of peracetic acid (D'Ans and Kneip, *Ber.*, 1915, **48**, 1144), aqueous sodium peroxide (O. Fischer and Trost, *ibid.*, 1893, **26**, 3083), acidified ammonium persulphate with a little silver nitrate as catalyst (O. N. Witt and Kopetschni, *ibid.*, 1912, **45**, 1134; compare Meisenheimer and Hesse, *Ber.*, 1919, **52**, 1162).

The use of other oxidising agents leads to a number of other types of compounds. Thus by choosing suitable conditions aniline yields azobenzene and azoxybenzene, phenylquinonedi-imine, $PhN{:}C_6H_4{:}NH$, emeraldine, aniline-black and *p*-benzoquinone. By mild conditions of oxidation, using lead peroxide and acetic acid and an ethereal solution of the amine, azobenzene and phenylquinonedi-imine are formed (S. Goldschmidt, *Ber.*, 1920, **53**, 28). The experimental evidence at present available appears to indicate that the polymerisation of phenylquinonedi-imine or its reaction with unchanged aniline may account for the occurrence of many of the complex products of the oxidation of aniline—such as emeraldine and aniline-black (Willstätter and C. W. Moore, *Ber.*, 1907, **40**, 2665; Majima and Aoki, *Ber.*, 1911, **44**, 3081; S. Goldschmidt and Wurschmitt, *ibid.*, 1922, **55**, 3220). It appears that the production of *p*-benzoquinone by the oxidation of aniline with chromic acid in aqueous solutions is preceded by the formation of aniline-black. (For views on the structure of aniline-black, the following papers should be consulted: Willstätter and Dorogi, *Ber.*, 1909, **42**, 2147, 4118; Green and S. Wolff, *ibid.*, 1911, **44**, 2571; Green and Woodhead, *J.*, 1910, **97**, 2388; 1912, **101**, 1117; *Ber.*, 1912, **45**, 1955). Actually, oxidation of aniline-black by dichromate and diluted sulphuric acid yields about 85% of the theoretical amount of *p*-benzoquinone; by oxidation with lead peroxide and sulphuric acid a 95% yield of *p*-benzoquinone is obtained.

Preparation of p-*Benzoquinone*.—A solution of 25 g. of aniline in a mixture of 200 g. of concentrated sulphuric acid and 750 c.c. of water is cooled by an external bath of ice and stirred mechanically. A solution of 25 g. of sodium dichromate in 100 c.c. of water is added slowly over a period of an hour, the temperature being kept below 10°. The mixture is kept over-night in a cool place, and then a solution of 50 g. of sodium dichromate in water is added gradually. The precipitate of aniline-black which has separated during the first part of the oxidation gradually dissolves with the production of a deep brown solution. About 4—5 hours after the final addition of the dichromate the solution is extracted three or four times with ether. The ethereal solution is dried in contact with anhydrous magnesium sulphate and the solvent distilled off. The residue of crude *p*-benzoquinone is purified by distillation in a current of steam. It is obtained as golden-yellow needles, m. p. 116°.

This method can be applied to the preparation of the homologues of *p*-benzoquinone. Thus *o*- or *m*-toluidine yield *p*-toluquinone; *p*-xylidine furnishes *p*-xyloquinone (Goldschmidt and Schmid, *Ber.*, 1885, **18**, 568; Nietski, *Annalen*, 1882, **215**, 158). Some amines with methyl groups *para* to the amino-group undergo oxidation with the elimination of the *para*-methyl to yield *p*-quinones. Thus mesidine yields 2 : 6-dimethyl-*p*-benzoquinone, ψ-cumidine yields *p*-xyloquinone (Nölting and T. Baumann, *Ber.*, 1885, **18**, 1150; compare Heymanns and Königs, *ibid.*, 1887, **20**, 2395).

(*e*) *Action of Nitrous Acid.*

The product of the reaction of amines with aqueous solutions of nitrous acid is determined largely by the type of amine, and the reaction is extensively used for the differentiation of amines. Secondary amines yield nitrosamines (iv). Tertiary amines undergo no reaction at the amino-group; but most of those containing an aryl group with an unsubstituted *para* position undergo nuclear substitution. The type of product from primary amines depends on the nature of the grouping attached to the primary amino-group. Aliphatic amines furnish, in the simplest cases, nitrogen and a hydroxy-compound (i), which latter may also yield other substances derived from it by rearrangement or dehydration.

Aromatic primary amines and many heterocyclic amino-compounds of the aromatic type yield diazonium salts (ii). α-Amino fatty esters and some α-keto-amines yield diazo-compounds (iii).

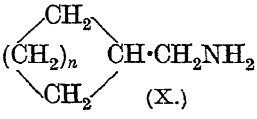
$$\begin{array}{rll} RR'{\cdot}CH{\cdot}NH_2 + HNO_2 & RR'CH{\cdot}OH + N_2 + H_2O & \text{(i)} \\ Ph{\cdot}NH_2{\cdot}HCl + HNO_2 & PhN_2Cl + 2H_2O & \text{(ii)} \\ R{\cdot}CH(NH_2){\cdot}CO_2Et + HNO_2 & R{\cdot}CN_2{\cdot}CO_2Et + 2H_2O & \text{(iii)} \\ RR'{\cdot}NH + HNO_2 & RR'N{\cdot}NO + H_2O & \text{(iv)} \end{array}$$

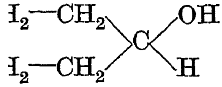
These reactions are probably preceded by the formation of the nitrite, which then undergoes decomposition in the directions indicated above; indeed, the nitrites of some amines have been isolated. Thus Wallach (*Annalen*, 1907, **353**, 318) has described the nitrites of menthylamine, pinylamine, and *m*-xylidine; Neogi (*J.*, 1914, **105**, 1270) has prepared the nitrites of several aliphatic amines.

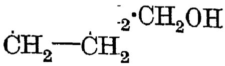
An interesting hypothesis to account for the production of the different products has been advanced by Oddo and Cesaris (*Gazzetta*, 1914, **44**, [ii], 209).

(1) *Primary Amines.* (a) *Aliphatic Amines.*—Aliphatic amines in general react with nitrous acid to give nitrogen. This applies not only to methylamine and its homologues, but also to amino-derivatives of the polymethylenes, benzylamine, and similar amines and amino-acids. Some exceptions are discussed in section (b) (p. 283). The evolution of nitrogen, when a primary amine is treated in cold aqueous acid solution with sodium nitrite, is used as a test for primary aliphatic amines. It also forms the basis of the Van Slyke method for the estimation of amino-acids. Although salts of methylamine or ethylamine react with sodium nitrite in aqueous solution according to equation I, the products from the higher homologues are more complex. Thus *n*-propylamine gives nitrogen and a mixture of *n*- and *iso*-propyl alcohols and propylene (V. Meyer and Forster, *Ber.*, 1876, **9**, 535; Linnemann, *Annalen*, 1872, **161**, 44; Siersch, *ibid.*, 1867, **144**, 140). *iso*Butylamine furnishes butylene, *iso*butyl alcohol, and *tert.*-butyl alcohol. The reaction of *n*-butylamine with nitrous acid has recently been examined quantitatively (Whitmore and Langlois, *J. Amer. Chem. Soc.*, 1932, **54**, 3441). *n*- and *sec.*-Butyl alcohols and *n*-butene are the principal products, the respective yields being 25, 13, and 37%; some *n*- and *sec.*-butyl chlorides are also formed. The higher aliphatic amines—as far as they have been examined—also furnish a mixture of olefin and isomeric alcohols (compare Freund and Lenze, *Ber.*, 1891, **24**, 2150; Freund and Schönfeld, *ibid.*, p. 3359). Allylamine, however, yields only nitrogen and allyl alcohol by the action of nitrous acid. Many primary amines containing a polymethylene ring suffer a more or less partial rearrangement by the action of nitrous acid. In amines of the type (X) (where $n = 1, 2, 3$, or 4) the ring is enlarged by the insertion of one carbon atom. Thus *cyclo*butane methylamine ($n = 1$) furnishes a mixture of

hydroxy*cyclo*pentane (XI) and *cyclo*butane methyl alcohol (XII) and unsaturated hydrocarbons (Demjanoff and Luschnikoff, *J. Russ. Phys. Chem. Soc.*, 1903, **35**, 26). This reaction has been used for the preparation of a higher ring system from a lower (Wallach, *Annalen*, 1907, **353**, 325; Ruzicka and Brugge, *Helv. Chim. Acta*, 1926, **9**, 399).


(X.)


(XI.)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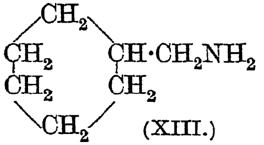
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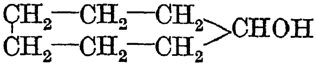
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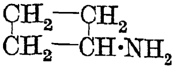
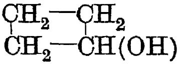
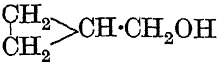

(XV.)

(XVI.)



(XVII.)

A further example of this is the formation of *cyclo*heptanol (XIV) from *cyclo*hexyl methylamine (XIII), some *cyclo*heptene being also formed (Ruzicka and Brugge, *loc. cit.*). The ring system in amino*cyclo*butane (XV) is, however, converted partly into a *cyclo*propane ring on treatment with nitrous acid, a mixture of (XVI) and (XVII) being formed (Demjanoff, *Ber.*, 1907, **40**, 4961). Amino*cyclo*propane under similar conditions gives allyl alcohol (Kischner, *J. Russ. Phys. Chem. Soc.*, 1905, **37**, 304).

(b) *Esters of α-Amino-Acids.*—The esters of α-aminoacetic acid react with nitrous acid under suitable conditions to yield diazoacetic esters (equation iii, p. 281). The same type of product is given by esters of α-aminopropionic, α-aminobutyric, and α-aminocaproic acids and by esters of α-aminophenylacetic and α-amino-β-phenylpropionic acids. Apparently the reaction is restricted to α-amino-esters. Amino groups in β- or γ-positions are replaced by hydroxyl groups (Curtius and Müller, *Ber.*, 1904, **37**, 1261; compare Curtius, *ibid.*, 1883, **16**, 2230; *J. pr. Chem.*, 1888, [ii], **38**, 401).

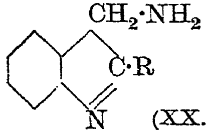
Preparation of Diazoacetic Ester.—Glycine ester hydrochloride (50 g.) and finely-powdered sodium nitrite (37·5 g.) are added to 100 c.c. of water in a 500-c.c. separating funnel. The mixture is shaken till the temperature has fallen to 0°, when 25 c.c. of ether are added and then a few drops of 10% sulphuric acid. The whole is now shaken thoroughly for a minute, when the lower aqueous layer is run into a flask cooled in ice. The ethereal solution is transferred to a dry flask. The aqueous layer is again placed in the separating funnel, mixed with a fresh quantity of 25 c.c. of ether, and the solution acidified by the addition of a few drops of 10% sulphuric acid. The mixture is shaken, the ether separated, and the whole operation repeated with fresh quantities of ether till the ethereal extracts are only feebly coloured. The united ethereal extracts are combined and washed with small quantities of sodium carbonate solution till the washings remain alkaline and have a deep yellow colour.

The ethereal solution is then dried in contact with calcium chloride. The ethereal solution is concentrated carefully in a warm water-bath and the last traces of solvent are removed by passing a current of air over the surface of the concentrated solution. Diazoacetic ester is a deep yellow liquid, b. p. 86°/88 mm.; it explodes on distillation at ordinary pressure (Curtius, *J. pr. Chem.*, 1888, [ii], **38**, 401; Silberrad, *J.*, 1902, **81**, 600).

Diazo-compounds are also formed from some α-amino-ketones, such as aminocamphor and α-aminoacetophenone (Angeli, *Ber.*, 1893, **26**, 1715; R. Schiff, *ibid.*, 1881, **14**, 1375). According to Angeli, the essential conditions for the formation of diazo-compounds from aliphatic amines is the presence of the grouping $X{:}\overset{|}{C}\cdot\overset{|}{C}H\cdot NH_2$ (where X may be C, O, or N) or $O{:}S\cdot\overset{|}{C}H\cdot NH_2$. Thus aminoacetonitrile (XVIII) and aminomethane disulphonic acid (XIX) yield diazo-compounds; (XX) behaves similarly (Angeli, *Ber.*, 1904, **37**, 2080; Curtius, *ibid.*, 1898, **31**, 2491; v. Pechmann and Manck, *ibid.*, 1895, **28**, 2377).

$NH_2\cdot CH_2\cdot CN$
(XVIII.)

$NH_2\cdot CH(SO_3H)_2$
(XIX.)



(XX.)

(c) *Aromatic Primary Amines.*—The salts of primary aromatic amines behave in a characteristic manner with nitrous acid. In cold aqueous solutions a diazonium salt is formed :

$$C_6H_5\cdot NH_2,HCl + HNO_2 \longrightarrow C_6H_5\cdot N_2\cdot Cl + H_2O$$

At higher temperatures the diazonium salt decomposes with the evolution of nitrogen and the formation of phenol.

The usual method of preparing an aqueous solution of a diazonium salt is to add the necessary amount of an aqueous solution of sodium nitrite to the amine dissolved in an excess of dilute mineral acid, cooled to 0° or − 10° by an external bath of ice and salt. Examples of these preparations are given in the section on diazo-compounds, pp. 334–348. This reaction is used for the detection of primary aromatic amines.

To a solution of about 0·1 g. of a suspected primary aromatic amine dissolved in 2 c.c. of 5*N*-hydrochloric acid and cooled to 0° by an ice-bath and by the addition of a small piece of ice to the solution, a dilute solution of sodium nitrite (14 g. in 1000 c.c. of water) is added till a slight excess of nitrous acid is present as shown by starch iodide paper. The solution should be clear. It is then poured into an alkaline solution of β-naphthol or R salt which has been largely diluted with aqueous ammonia.

The formation of a bright red, orange-red, or reddish-blue precipitate from β-naphthol solution or a similarly coloured solution from R salt indicates the presence of a diazonium salt derived from a primary aromatic amine.

Preparation of diazonium salts in aqueous solution is usually satisfactory with aniline and its homologues, their simple substitution products and with the naphthylamines. It fails, however, when the amine contains a number of negative substituents in the nucleus. Thus trinitroaniline and pentabromoaniline give no diazo-compounds by this process. In these circumstances special methods must be employed which usually involve the use of an excess of moderately concentrated sulphuric acid; less frequently concentrated hydrobromic acid or fuming hydrochloric acid. Claus's method consists in dissolving the base in a moderate excess of sulphuric acid monohydrate, cooling to − 10°, and then adding to the stirred solution the calculated amount of nitrosylsulphuric acid (Claus and Wallbaum, *J. pr. Chem.*, 1897, [ii], **56**, 48; Claus and Beysen, *Annalen*, 1891, **266**, 224). When this process is not satisfactory, as is the case with some tetrabromo-substituted amines, fuming hydrochloric acid or concentrated hydrochloric acid has been used instead of the monohydrate of sulphuric acid (Claus and Wallbaum, *loc. cit.*, p. 51).

Even under the conditions just described, amines such as picramide cannot be diazotised, but conditions for the successful diazotisation of such amines have been described by Misslin (*Helv. Chim. Acta*, 1920, **3**, 626). The amine is dissolved in glacial acetic acid and then treated with nitrosylsulphuric acid diluted with a moderate excess of concentrated sulphuric acid. The excess of concentrated sulphuric acid is necessary, for in its absence no diazotisation occurs.

Preparation of 2 : 4 : 6-*Trinitrobenzenediazonium Sulphate and of* 2 : 4 : 6-*Benzeneazo-β-naphthol.*—Picramide (2·3 g.) is dissolved in 160 c.c. of warm glacial acetic acid and the solution cooled to 17°. A solution of nitrosylsulphuric acid (prepared by dissolving 0·7 g. of sodium nitrite in 160 g. of sulphuric acid monohydrate at 45°) is then added cautiously over a period of 25 minutes, while the temperature of the solution is brought to 0—3° by external cooling and stirring. A viscous pale yellow solution of the diazonium salt is thus obtained. It scarcely couples with alkaline R salt.

For the preparation of the azo-β-naphthol, a solution of 2 g. of β-naphthol in 15 c.c. of glacial acetic acid is added to the diazonium solution. A very intense colour develops, and after a few minutes the solution is poured into ice-water. A brown flocculent precipitate is obtained. It is collected by filtration, washed with water, and extracted with boiling alcohol The residue is the crude azo-compound, which is purified by crystallisation from acetic acid or nitrobenzene (Misslin, *loc. cit.*).

Preparation of a Solution of 2 : 6-*Dinitro*-4-*methylbenzenediazonium Sulphate.*—2 : 6-Dinitro-*p*-toluidine is dissolved in twice its weight of concentrated sulphuric acid, and after cooling in ice, ice-water is added till a faint turbidity results. The solution is then stirred mechanically, cooled to 0°, and powdered sodium nitrite (calc. amount) added (Claus and Beyson, *loc cit.*).

O. N. Witt (*Ber.*, 1909, **42**, 2953) has described conditions for the diazotisation of some negatively-substituted anilines by which a solution of the amine in concentrated nitric acid is treated with potassium metabisulphite.

The capacity to yield diazonium salts is not confined to amino-derivatives of the aromatic hydrocarbons, but is shared by some amino-substituted heterocyclic compounds. Thus 4-aminotriazole and its homologues (Thiele and Manchot, *Annalen*, 1898, **303**, 40), 4-aminothiazole (Traumann, *ibid.*, 1888, **249**, 39; Schatzmann, *ibid.*, 1891, **261**, 9; Hantzsch and Popp, *ibid.*, 1889, **250**, 274; Wohmann, *ibid.*, 1890, **259**, 279), aminoantipyrine (Knorr and Stolz, *ibid.*, 1896, **293**, 68), have been shown to diazotise in aqueous solution, and to couple and yield azo-compounds. In spite of the comparative instability of the diazo-compounds derived from triazoles and thiazoles, the classical work of Morgan and Reilly and their associates has shown that the pure diazonium salts can be isolated (Morgan and Reilly, *J.*, 1913, **103**, 808, 1494; *ibid.*, 1914, **105**, 435; Morgan and Morrow, *ibid.*, 1915, **107**, 1291; Morgan and Reilly, *ibid.*, 1916, **109**, 155). Diazonium salts have also been prepared from 5-amino-3 : 5-dimethyl*iso*oxazole (Morgan and Burgess, *ibid.*, 1921, **119**, 697, 1546). Other amino-heterocyclic compounds which have been shown to diazotise are 3-aminoquinoline (W. H. Mills and Watson, *J.*, 1910, **97**, 753), and aminotetronic acid (Wolff and Lüttringhaus, *Annalen*, 1900, **312**, 143). Although 3-aminopyridine diazotises normally (Mohr, *Ber.*, 1898, **31**, 2495), 2-aminopyridine appears to give diazo-salts which are unstable in aqueous solution (Tschitschibabin and Zeide, *J. Russ. Phys. Chem. Soc.*, 1915, **46**, 1216). Measurements of the stability of diazonium salts from aminopyrazoles, pyrazolones, and triazoles have been made by Reilly and Madden (*J.*, 1925, **127**, 2936; 1929, 815).

The normal production of diazonium salts in the benzene series may be disturbed by the presence of other reactive groupings in the aromatic nucleus. Thus the action of nitrous acid on *o*- and *p*-aminophenols may lead to the formation of internal condensation products—diazo-oxides. The *m*-aminophenols do not appear to yield such compounds. On the other hand, 8-amino-α-naphthol forms a diazo-oxide. The tendency to diazo-oxide formation appears to depend on the conditions and on the other groups present. Thus while *o*- and *p*-aminophenols yield normal diazonium salts in acid solution, many halogen and nitro-substituted aminophenols furnish diazo-oxides readily in acid solution. The diazo-oxides in general are highly coloured crystalline solids which couple with β-naphthol to give azo-compounds and form highly coloured salts in alkali. Diazo-oxides may also result by the elimination of halogen or nitro-groups in the *ortho* or *para* position to the diazo-grouping, if other negative groups are also present. This is usually effected by neutralising with alkali or by adding sodium acetate (Morgan and J. W. Porter, *J.*, 1915, **107**, 645; Morgan and Tomlins, *ibid.*, 1917, **111**, 497; Morgan and Evens, *ibid.*, 1919, **115**, 1126; Orton, *J.*, 1903, **83**, 796).

The behaviour of diamines towards nitrous acid is considered in section 2 (p. 297).

2. *Secondary Amines.*—All secondary amines, whether aliphatic, aromatic, or mixed aliphatic aromatic amines, react with nitrous acid to yield nitrosamines.

$$\mathrm{RR'NH + HONO \longrightarrow RR'N{\cdot}NO + H_2O.}$$

The reaction is brought about by adding the calculated amount of an aqueous solution of sodium nitrite to the amine in aqueous acid. The preparation is illustrated by the following.

Preparation of Dimethylnitrosamine.—A solution of 180 g. of sodium nitrite in 200 c.c. of warm water is added slowly to 200 g. of dimethylamine dissolved in 100 c.c. of water acidified with sulphuric acid. When all the nitrite has been added, the solution is distilled almost to dryness. The distillate is acidified and distilled again to remove traces of unchanged amine. The addition of solid potassium carbonate to the distillate causes the nitrosamine to separate as a pale yellow oil. This is removed and dried in contact with solid potassium carbonate. The dry nitrosamine distils at 148° (Renouf, *Ber.*, 1880, **13**, 2170).

Preparation of Nitrosopiperidine.—A solution of piperidine in four times its weight of 25% sulphuric acid is cooled to 0° and the calculated amount of iodium nitrite in water added slowly. The nitrosamine separates as an oil which is taken up in ether and washed with concentrated potash solution. Evaporation of the solvent leaves nitrosopiperidine as a yellow oil, b. p. 218°.

Preparation of Diphenylnitrosamine.—A solution of 50 g. of diphenylamine in 250 g. of alcohol is cooled to 0° and 35—40 c.c. of concentrated hydrochloric acid are added all at once. Before the hydrochloride of diphenylamine can separate, a solution of 25 g. of sodium nitrite in 35 c.c. of water is added rapidly and the mixture stirred. The precipitated nitrosamine is collected by filtration and purified by crystallisation from hot light petroleum (b. p. 80—100°). It is obtained as massive pale yellow crystals, m. p. 66—67° (compare Vanino, *Präparative Chemie*, II, 666).

Preparation of Phenylethylnitrosamine.—A solution of ethylaniline in 2 mol. proportions of dilute hydrochloric acid, cooled to 0°, is treated with aqueous sodium nitrite. A turbidity is first produced, which gives place to the separation of an oil as more nitrite is added. When the mixture contains a slight excess of free nitrous acid the nitrosamine is extracted with ether and the ethereal solution washed first with aqueous alkali, and then with water. It is finally dried over anhydrous magnesium sulphate. Evaporation of the solvent leaves phenylethyl nitrosamine as a yellowish oil which can be further purified by steam distillation or by distillation under reduced pressure (at about 1—0·5 mm.).

This method can be applied generally to the preparation of the mixed aryl alkylnitrosamines. It is advisable, however, to avoid prolonged contact of the nitrosamine with aqueous acid, for a few aryl alkylnitrosamines, such as those derived from the alkyl-*o*-toluidines, readily pass, under the influence of aqueous hydrochloric acid, into the corresponding *p*-nitrosamines (O. Fischer and Diepolder, *Annalen*, 1895, **286**, 163).

Preparation of o-*Tolylmethylnitrosamine.*—A solution of 24 g. of methyl-*o*-toluidine in 31 g. of concentrated hydrochloric acid and 70 g. of water is treated with 14·5 g. of sodium nitrite in water. The nitrosamine is taken up in ether and purified in the usual manner.

Preparation of 5-*Nitroso-ethyl-*o*-toluidine.*—A solution of 10 g. of ethyl-*o*-toluidine in 40 c.c. of concentrated hydrochloric acid is cooled and a concentrated aqueous solution of 5 g. of sodium nitrite added, while the mixture is stirred. When all the nitrite has been added, about 20 g. of hydrochloric acid are added and the solution is kept till the oily nitrosamine has dissolved. The solution is then cautiously diluted with water and neutralised with aqueous ammonia. The nitroso-base separates out, and is collected either by filtration or by solution in ether. It crystallises from benzene as green leaflets, m. p. 140°—yield about 10 g. (O. Fischer and Diepolder, *loc. cit.*).

3. *Tertiary Amines.*—In aqueous solution the tertiary aliphatic amines do not react with nitrous acid, and can be recovered from such mixtures unchanged. The dialkylanilines, however, undergo substitution in the nucleus with the formation of *p*-nitroso-compounds. This reaction is shared by many nuclear-substituted dialkylanilines, but it is essential that the *para* position should be free.

Preparation of p-*Nitrosodimethylaniline.*—Dimethylaniline (24 g.) is dissolved in 50 c.c. of concentrated hydrochloric acid mixed with an equal volume of water. After cooling the solution in ice, sodium nitrite (14 g.) dissolved in a small quantity of water is added slowly, while the solution is stirred. *p*-Nitrosodimethylaniline hydrochloride soon commences to separate as an orange-yellow crystalline paste. The mixture is kept after the addition of all the nitrite till no further separation takes place. The hydrochloride is then filtered off and washed with dilute hydrochloric acid. The free base is obtained by suspending the hydrochloride in water and adding dilute aqueous alkali. The base is taken up in ether, the ethereal solution washed with water, dried in contact with anhydrous magnesium sulphate, and the solvent evaporated. *p*-Nitrosodimethylaniline is obtained as green plates, m. p. 85°.

It is noteworthy that the presence of substituents in the *ortho* position to the dialkylamino-group hinders the formation of *p*-nitroso-compounds. Thus dimethyl-*o*-toluidine, 3-dimethylamino-*o*-xylene, and dimethylamino-*p*-xylene do not react with nitrous acid to any appreciable extent (v. Braun, Arkuszewski and Köhler, *Ber.*, 1918, **51**, 282). *o*-Chlorodimethylaniline also is indifferent to aqueous nitrous acid (Friedländer, *Monatsh.*, 1898, **19**, 627), and *o*-dimethylaminobenzoic esters are also stated to form no nitroso-derivatives (Houben, *Ber.*, 1909, **42**, 3188). Dialkylanilines containing a tertiary alkyl group also fail to form *p*-nitroso-derivatives. Thus methyl-*tert.*-butylaniline is recovered unchanged after keeping in a dilute aqueous solution of nitrous acid for $\frac{1}{2}$ hour (Hickinbottom, *J.*, 1933, 946).

(*f*) *Replacement of the Amino-group by Hydroxyl by Hydrolysis.*

The amino-group of the alkylamines and of aniline and its homologues is firmly bound; it is resistant to the action of boiling aqueous alkalis or aqueous acids. The stability of the amino-group of aniline is modified by the introduction of suitable substituents into the nucleus. This is particularly marked with the nitroso-group. Thus *p*-nitrosoaniline is converted into *p*-nitrosophenol and ammonia by boiling with aqueous alkali. The *p*-nitrosomono- and di-alkylanilines similarly yield *p*-nitrosophenol and alkylamines (O. Fischer and E. Hepp, *Ber.*, 1879, **20**, 2474; 1888, **21**, 684; Baeyer and Caro, *ibid.*, 1874, **7**, 964).

$$ON{\cdot}C_6H_4{\cdot}NH_2 + KOH \qquad ON{\cdot}C_6H_4{\cdot}OK + NH_3.$$

Nitro-groups situated in *o*- and *p*-positions with respect to the amino also render the amino-group susceptible to alkaline hydrolysis. The effect is, however, much less marked than with the nitroso-group. Thus *p*-nitrodimethylaniline is unchanged by boiling with aqueous alkali (Weber, *Ber.*, 1877, **10**, 761). The amino-group is comparatively easily hydrolysed if there are two or three groups in the *ortho* and *para* positions. Thus 2 : 4-dinitro- and 2 : 4 : 6-trinitro-anilines yield the corresponding phenols by the action of hot aqueous alkali (Pisani, *Annalen*, 1854, **92**, 326; Willgerodt, *Ber.*, 1876, **9**, 979).

In contrast to the comparative stability of aniline and its homologues, the naphthylamines are hydrolysed to naphthols and ammonia by heating with aqueous acids or alkalis (Franzen and Kempf, *Ber.*, 1917, **50**, 101; Meister, Lucius, and Brüning, D.R.-P. 74,879: 76,595; E.P. 14,301/1892). Aqueous solutions of sodium bisulphite are particularly effective in bringing about this hydrolysis (Bucherer, *J. pr. Chem.*, 1904, [ii], **69**, 49). This method has been applied to the industrial preparation from the naphthylaminesulphonic acids of some naphtholsulphonic acids which are not conveniently obtained by the direct sulphonation of the naphthol.

(*g*) *Action of Nitric Acid.*

Aliphatic amines furnish the nitrate by treatment with nitric acid. In general, no further action is to be expected with aqueous nitric acid. The nitrates of secondary aliphatic amines can be dehydrated by the action of acetic anhydride with the formation of secondary nitramines.

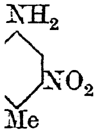
$$(CH_3)_2NH,HNO_3 \longrightarrow (CH_3)_2N{\cdot}NO_2 + H_2O.$$

Dry dimethylamine nitrate yields dimethylnitramine by shaking it with acetic anhydride at room temperature; piperidine nitrate furnishes nitropiperidine by warming with acetic anhydride (Bamberger and Kirpal, *Ber.*, 1895, **28**, 535). The nitrates of primary aliphatic amines do not give a satisfactory yield of nitramine by this method. It has, however, been applied successfully to the preparation of arylnitramines. Thus aniline nitrate, treated with acetic anhydride, yields phenylnitramine. Many of the homologues of aniline behave similarly (Bamberger, *Ber.*, 1895, **28**, 399). The reaction is sometimes met with during the nuclear nitration of arylamines in presence of acetic anhydride.

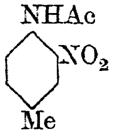
Preparation of 2 : 4 : 6-*Trichlorophenylnitramine.*—Trichloraniline (50 g.) is dissolved in 450 c.c. of acetic acid. To the solution are added 40 c.c. of nitric acid (90%) which has been freed from nitrous acid by adding urea nitrate. The solution is then cooled to 12°, and 30 c.c. of acetic anhydride are slowly added. When the precipitate of trichloraniline nitrate has dissolved, the solution is poured into 600 c.c. of ice-water. The precipitated nitramine is collected, washed with water, and freed from a small amount of impurity by solution in sodium carbonate. The nitramine is precipitated from the filtered solution by adding dilute hydrochloric acid, washed, and dried (Orton and A. E. Smith, *J.*, 1905, **87**, 393).

The introduction of a nitro-group into the nucleus of arylamines can be effected comparatively readily. If nitric acid either alone or in acetic acid solution is used as the nitrating agent, it is usually advisable to protect the primary or secondary amino-group by acylation. Instead of using nitric alone, a mixture of nitric and sulphuric acids can be employed. It should be noted, however, that the sulphuric acid may have an important effect on the position assumed by the nitro-group. This is well illustrated in the nitration of *p*-toluidine. In a large excess of sulphuric acid, 2-nitro-*p*-toluidine (XXI) is formed by the action of one molecular proportion of nitric acid. The nitration of acet-*p*-toluidide yields 3-nitroaceto-*p*-toluidide (XXII). The alkyl derivatives of *p*-toluidine behave similarly. Aniline in a large excess of sulphuric acid is nitrated with one molecular proportion of nitric acid to give a mixture of *m*- and *p*-nitranilines, while acetanilide furnishes a mixture of *o*- and *p*-nitroacetanilides (Nölting and Collin, *Ber.*, 1884, **17**, 261).

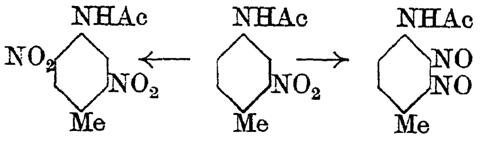
Another example of the influence of the medium in nitration is the formation of 2 : 3-dinitroacet-*p*-toluidide (XXV) from 2-nitroaceto-*p*-toluidide by the action of fuming nitric acid; nitration with nitric–sulphuric acid mixture furnishes the isomeric 2 : 5-dinitroaceto-*p*-toluidide (XXIV) (Scott and Robinson, *J.*, 1922, **121**, 844).



(XXI.)



(XXII.)



(XXIV.) (XXIII.) (XXV.)

The following illustrate some of the methods used for the nitration of arylamines.

Preparation of p-*Nitroformanilide*.—Formanilide dissolved in 2 parts of concentrated sulphuric acid is nitrated by adding it to 1 part of cold concentrated nitric acid (*d* 1·42) diluted with an equal volume of concentrated sulphuric acid. The mixture is kept at 15—20° and stirred during the nitration. The product is precipitated by pouring on ice. The yellow crystalline solid is collected, washed with water, dried, and crystallised from toluene, m. p. 196° (Morgan and Upton, *J.*, 1917, **111**, 190).

Preparation of 3- *and* 5-*Nitro*-o-*toluidines*.—Aceto-*o*-toluidide (20 g.) is added in small portions at a time to 75 c.c. of nitric acid, the temperature being kept below 20°. When all the acetyl derivative has been added, the temperature is raised to 40—50° and kept at this point for ¾—1 hour. It is then poured into water, the resulting precipitate washed and dried—yield 14 g. The product is a mixture of 5-nitroaceto-*o*-toluidide and the 3-nitroaceto-compound.

The mixed nitro-compounds are covered with 50 c.c. of concentrated hydrochloric acid and steam distilled, till no more orange-coloured crystals collect in the receiver. These consist of 3-nitro-*o*-toluidine, m. p. 97°. On adding an excess of sodium carbonate to the residue in the flask, a precipitate of crude 5-nitro-*o*-toluidine results. It is collected by filtration, washed with water, and crystallised from alcohol, m. p. 133° (Cohen and Dakin, *J.*, 1901, **79**, 1127; Page and Heasman, *ibid.*, 1923, **123**, 3238).

Preparation of 2 : 5-*Dinitro-aceto*-p-*toluidide.*—2-Nitroaceto-*p*-toluidide (5·1 g.) is dissolved in the minimum amount of concentrated sulphuric acid, cooled to 0°, and nitrated by the addition of a solution of potassium nitrate (5·2 g.) in a small amount of sulphuric acid. When all the nitrating solution has been added, the mixture is kept at 0° for 2 hours, and then added to ice-water. The precipitate of crude acetyl derivative is thoroughly washed with water and then crystallised from warm alcohol. It separates from this solvent as colourless aggregates of slender needles, m. p. 132—133° (Scott and Robinson, *loc. cit.*, p. 845).

Preparation of 4-*Nitro*-o-*toluidine.*—A solution of 30 g. of *o*-toluidine in about 450 g. of concentrated sulphuric acid is cooled to 0° and nitrated by the addition of 28 g. of 63% nitric acid in 100 g. of concentrated sulphuric acid. The mixture is stirred during the nitration and subsequently kept for 2 hours at room temperature. It is then poured on 600 g. of ice, and the mixture stirred. The greater part of the ice melts and an almost clear solution results, which in a short time sets to a thick paste of yellow crystals. The crystalline magma, which consists of the sulphate of 4-nitro-*o*-toluidine, is collected at the pump and thoroughly drained. It is then stirred with a slight excess of alkali. 4-Nitro-*o*-toluidine separates in an almost pure condition. It is collected, washed with water, and crystallised from alcohol—yellow prisms, m. p. 107°, yield 34 g. (Ullman and Grether, *Ber.*, 1902, **35**, 337).

Preparation of 2-*Nitro*-p-*toluidine.*—A solution of 10 g. of *p*-toluidine in 200 g. of concentrated sulphuric acid is cooled in a freezing mixture till the temperature is below 0°. It is then stirred, and a solution of 7·5 g. of nitric acid (*d* 1·48) in 30 g. of sulphuric acid added. The temperature of the reaction mixture is kept below 0° till the whole of the nitrating acid has been added. After several hours, the mixture is poured into about 500 c.c. of ice-water, filtered, and diluted to 1500 c.c. 2-Nitro-*p*-toluidine is precipitated by neutralising with sodium carbonate. The product is collected, washed with water, and then crystallised from dilute alcohol, m. p. 77°—yield, 10 g. (Nölting and Collin, *loc. cit.*).

Preparation of 2-*Nitrodimethyl*-p-*toluidine.*—Dimethyl-*p*-toluidine dissolved in 12 parts of concentrated sulphuric acid is nitrated by gradually adding 2 mol. proportions of nitric acid diluted with an excess of concentrated sulphuric acid. The reaction mixture is stirred during the addition of the nitric acid solution. After keeping for 12 hours the mixture is poured on ice and neutralised by adding dilute ammonia. 2-Nitrodimethyl-*p*-toluidine is collected by filtration and washed with water, m. p. 27° (Morgan and Clayton, *J.*, 1910, **97**, 2650).

It is interesting to note that under the conditions described above only a mononitro-derivative is formed, although an excess of nitric acid has been used. If the temperature rises unduly when the reaction mixture is poured into water, the product is 2 : 5-dinitrodimethyl-*p*-toluidine.

During the nitration of dialkylarylamines, one of the alkyl groups may be replaced by $-NO$ or $-NO_2$. This usually occurs during the vigorous conditions of nitration.

Preparation of 2 : 4 : 6-*Trinitrophenyl*-n-*butylnitramine from Di*-n-*butylaniline.*—The tertiary amine is added cautiously to ten times its weight of fuming nitric acid mixed with an equal weight of acetic acid. The mixture is stirred during the addition of the amine. The reaction is completed by warming on a water-bath till the dark colour of the solution has changed to a pale yellow or red. It is then poured on ice, and the precipitate collected. The nitramine is obtained pure by dissolving it in cold fuming nitric acid and allowing the solution to crystallise at room temperature over several hours or even days. The nitramine may then be crystallised from glacial acetic acid—very pale yellow plates, m. p. 100°.

This method has been used for other dialkyl anilines (Reilly and Hickinbottom, *J.*, 1920, **117**, 135).

Preparation o 2 : 4 : 6-*Trinitro*-m-*tolylmethylnitramine.*—4 : 6-Dinitrodimethyl-*m*-toluidine (40 g.) is added in small quantities at a time to 100 c.c. of fuming nitric acid warmed to 50°. When all the solid has been added the mixture is heated in a water-bath till the evolution of brown fumes ceases. The mixture is then cooled and water added. The nitramine separates as an oil, which gradually solidifies. It is washed with water and crystallised from alcohol containing a little acetic acid, m. p. 101° (Brady and W. H. Gibson, *J.*, 1921, **119**, 102).

A similar result can be obtained by nitration with fuming nitric acid in presence of sulphuric acid. This type of process was formerly used for the technical preparation of 2 : 4 : 6-trinitrophenylmethylnitramine from dimethylaniline.

Nitration of dialkylanilines may also be accomplished by the use of tetranitromethane in presence of boric acid (E. Schmidt and Heinrich Fischer, *Ber.*, 1920, **53**, 1529). If a solution of tetranitromethane in pyridine solution is used, one of the alkyl groups is displaced by –NO without the introduction of nitro-groups into the nucleus (see p. 275).

*Preparation of 3-Nitrodimethyl-*p*-toluidine.*—Dimethyl-*p*-toluidine (20 g.) dissolved in 20 c.c. of alcohol is added to a solution of 9·2 g. of boric acid dissolved in 60 c.c. of alcohol. The solution is cooled in ice, while 30·5 g. of tetranitromethane diluted with 20 c.c. of alcohol are added gradually. The mixture is kept in ice for 1 hour after all the tetranitromethane has been added. The separation of a crystalline product will then be complete. After 2 hours it is collecten by filtration and washed with a little alcohol. It consists of the nitroform salt of 3-nitrodimethyl-*p*-toluidine.

This product (24 g.) is added to a mixture of 17 c.c. of 30% sodium carbonate solution and 45 c.c. of water warmed on a water-bath. The crystals decompose to yield an oil which is distilled in steam. It is isolated from the distillate by extraction with ether, the extract dried in contact with sodium sulphate and fractionated. 3-Nitrodimethyl-*p*-toluidine is collected at 110—113/0·5 mm.—yield 11·7 g. (Schmidt and Fischer, *loc. cit.*).

(h) *Action of Halogens.*

Arylamines react with halogens comparatively readily, and under suitable conditions yield nuclear-substituted products. Halogenation of the primary or secondary amines is usually effected by means of bromine or chlorine acting on an acetic acid solution of the amine, or in such aqueous media as hydrobromic or hydrochloric acids, or even in water. Less rarely alcohol, ether, chloroform, or carbon disulphide is used. The reaction in these media is generally less satisfactory than in acetic acid.

Preparation of 4 : 6-Dichloro-2-bromoaniline.—A solution of *o*-bromoaniline in 20% hydrochloric acid is treated with a freshly-prepared solution of 2 mol. proportions of chlorine dissolved in 20% hydrochloric acid. The addition of water precipitates 4 : 6-dichloro-2-bromoaniline, m. p. 82° (Reed and Orton, *J.*, 1907, **91**, 1552).

Preparation of 4-Bromodimethylaniline.—The calculated amount of bromine is added to dimethylaniline dissolved in acetic acid containing some water. When all the bromine has been added, the mixture is kept for some time, then diluted with water, and the greater part of the acid neutralised with ammonia. The amine separates out in a crystalline condition, m. p. 55—56° (Fries, *Annales*, 1906, **346**, 187).

Preparation of 4-Bromoaniline.—A solution of 5 g. of aniline in 25 c.c. of acetic acid is cooled and stirred mechanically, while 8 g. of bromine in 35 c.c. acetic acid are added at the rate of about 1½ c.c. every minute. When the bromination is complete, aqueous sodium acetate is added to completely precipitate the base. It is purified by crystallisation from 60% alcohol, and is obtained as colourless needles, m. p. 66° (Fuchs, *Monatsh.*, 1915, **36**, 138).

Preparation of 2 : 4 : 6-Tribromo-3-nitroaniline.—A solution of 7 g. of bromine in 30 c.c. of acetic acid is added to a stirred and cooled solution of 3·3 g. of *m*-nitroaniline in 15 c.c. of acetic acid. After keeping at room temrature for a short time, the product is precipitated by adding water—yield g.; yellow needles, m. p. 102—103°, from alcohol (Fuchs, *loc. cit.*, p. 133).

*Preparation of 3 : 5-Dibromo-*p*-toluidine.*—*p*-Toluidine (5 g.) in 20 c.c. of acetic acid is treated with 9 g. of bromine in 40 c.c. of acetic acid. After completion of the bromination, the hydrobromide of the base is precipitated by adding water. The free base—m. p. 79°—is obtained by adding sodium acetate to a suspension of the salt in water (Fuchs, *loc. cit.*, p. 118).

Preparation of 2 : 4-Dichloroacetanilide.—A solution of 100 g. of acetanilide in 800 c.c. of glacial acetic acid is mixed with 131 g. of fused sodium acetate in a flask and the whole weighed. Chlorine is then passed into the cold mixture. As soon as *p*-chloroacetanilide commences to separate, the flask is heated in a water-bath and the stream of chlorine continued till the increase in weight corresponds with the absorption of 2 mol. proportions of chlorine. A few c.c. of an aqueous solution of sulphur dioxide are then added to reduce any chloramine which may have been formed.

On cooling, 2 : 4-dichloroacetanilide and sodium chloride separate. The precipitate is then collected and washed with water. A further amount of dichloroacetanilide is obtained by diluting the original filtrate with half its volume of warm water, m. p. 145°—yield theoretical (Reed and Orton, *J.*, 1907, **91**, 1553).

Preparation of 2 : 4 : 6-Tribromoethylaniline.—A solution of 12 g. of ethylaniline in 50 c.c. of acetic acid is treated with 45 g. of bromine. After adding some water, the mixture is kept overnight, when the red colour of the solution will have disappeared. The paste of crystals which has separated is collected, washed with acetic acid, and then treated with ammonia. The amine thus obtained is crystallised from alcohol or acetic acid, m. p. 45° (Fries, *Annalen*, 1906, **346**, 183).

It is interesting to note that dimethylaniline, treated with bromine under similar conditions, loses a methyl group with the formation of 2 : 4 : 6-tribromomethylaniline (Fries, *loc. cit.*, p. 192).

An alternative method for the regulated chlorination of primary arylamines is by the reaction of the acetyl derivative of the amine with the necessary amount of hypochlorous acid. This can be effected very conveniently by the addition of bleaching-powder to an acetic acid solution of the acetyl derivative.

Preparation of 2- and 4-Chloroaniline.—A solution of bleaching-powder (1 mol. proportion) is slowly added to a solution of 50 g. of acetanilide in 500 c.c. of acetic acid over a period of 1 hour, the mixture being stirred and maintained at 8° throughout the operation. After keeping overnight, the greater part of the *p*-chloroacetanilide has separated in a crystalline form. It is collected by filtration and purified by crystallisation, m. p. 173—175°—yield 25 g.

The filtrate from the *p*-chloroacetanilide and the mother-liquors from the crystallisation are mixed with sufficient concentrated hydrochloric acid to give a 10% solution of hydrogen chloride. The mixture is then boiled for several hours to hydrolyse the acetyl derivatives, then made alkaline and distilled in steam. *p*- and *o*-Chloroaniline and some 2 : 4-dichloroaniline are isolated from the distillate by means of ether. The separation of the *para*-isomer is effected by mixing the amines with a slight excess of 3% sulphuric acid and steam distilling, so that the concentration of acid remains constant. *o*-Chloroaniline and 2 : 4-dichloroaniline pass over, while *p*-chloroaniline remains behind as sulphate. The amines from the distillate are dissolved in the least excess of 3—5% sulphuric acid and the solution is cautiously neutralised with 10% sodium hydroxide. Dichloroaniline separates out and is collected by filtration. The addition of an excess of alkali to the filtrate liberates pure 2-chloroaniline, b. p. 208—209° (W. J. Jones and Orton, *J.*, 1909, **96**, 1058).

An interesting method of chlorination consists in the use of a chloroamine as the source of chlorine. This method has been used when the usual process of treatment with chlorine is too drastic.

Preparation of 2 : 6-Dichloro-4-bromoaniline.—Acetyl chloroamino-2 : 4-dichlorobenzene (5·8 g.—2 mol. proportions) in 15 c.c. of chloroform is added to *p*-bromoaniline (2 g.—1 mol. proportion) in 15 c.c. of chloroform. The mixture is gently warmed, but care must be taken, as the subsequent reaction may be too violent. When the reaction is complete, the solution is cooled, when some of the 2 : 4-dichloroacetanilide (which results from the acetylchloroamino-2 : 4-dichlorobenzene) separates. It is filtered off and the filtrate saturated with dry hydrogen chloride. The precipitate thus formed is collected, washed with chloroform and boiled with 75% alcohol containing 5% of concentrated hydrochloric acid. 2 : 6-Dichloro-4-bromoaniline separates on cooling—m. p. 85° (Reed and Orton, *loc. cit.*).

The introduction of iodine into the nucleus of aromatic amines can be effected by the action of elementary iodine on the amine, preferably in presence of calcium carbonate or in acetic acid solution. A more satisfactory method consists in adding the necessary amount of iodine chloride to the amine or its acetyl derivative (Michael and Norton, *Ber.*, 1878, **11**, 107). Thus 2 molecular proportions of iodine monochloride react with 1 molecular proportion of aniline in acetic acid solution to furnish 2 : 4-di-iodoaniline. With 3 molecular proportions of iodine monochloride, 2 : 4 : 6-tri-iodoaniline is formed.

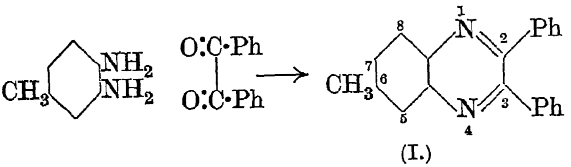
Preparation of p-*Iodoacetanilide.*—A solution of iodine monochloride is prepared by passing the necessary amount of chlorine into 15 g. of acetic acid containing 12·7 g. of iodine. It is mixed with a solution of 13·5 g. of acetanilide in 15 g. of acetic acid. The reaction is complete when *p*-iodoacetanilide has ceased to separate. The reaction mixture is then diluted with 200 c.c. of water, the precipitate collected, washed with dilute alkali and water, and then crystallised from alcohol, m. p. 184° (Chattaway and Constable, *J.*, 1914, **105**, 124).

It has been observed that during bromination, and to a less extent during chlorination, one or more of the groups in the nucleus may be replaced by halogen. Thus by the chlorination of *p*-bromoaniline, a mixture of dichlorobromoaniline and trichloroaniline is formed; 2 : 4-dibromoaniline yields tribromoaniline and dichlorobromoanilines on chlorination (Reed and Orton, *loc. cit.*). Other examples of the replacement of bromine by chlorine are given by Chattaway and Orton (*J.*, 1901, **79**, 822). The replacement of sulphonic groups in halogenated sulphanilic acids by bromine or chlorine is discussed on p. 398.

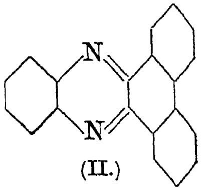
(2) *Special Reactions of Diamines.*

(a) The 1 : 2-*diamines* possess the amino-groups attached to adjacent carbon atoms. The term is here used to denote aliphatic as well as aromatic diamines. The aromatic 1 : 2-diamines are distinguished from other aromatic diamines by the ease with which ring formation occurs, but in the aliphatic series the distinction is not so definite, so that many reactions in the aromatic series which conclusively establish the presence of a 1 : 2-diamine can only be applied to aliphatic diamines with reservations.

Formation of Quinoxalines.—Aromatic diamines with the amino-groups in the *ortho* position condense with 1 : 2-diketones with the formation of azines (Hinsberg, *Annalen*, 1887, **237**, 327).



(I.)



(II.)

Benzil and phenanthraquinone are most frequently employed for this purpose, the condensation being generally effected in alcoholic or acetic acid solution. The product can be recognised by the production of an intense brownish-red, red, or reddish-blue coloration with concentrated sulphuric acid.

Preparation of 2 : 3-*Diphenyl-*6-*methylquinoxaline* (I).—Equivalent amounts of 3 : 4-toluylene diamine and benzil in hot alcoholic solution are mixed and heated gently for a short time. The quinoxaline separates on dilution as platelets with a silvery lustre, m. p. 111° (Hinsberg, *loc. cit.*, p. 340).

Preparation of Phenanthrazine (II).—An alcoholic solution of *o*-phenylenediamine is mixed with the equivalent amount of phenanthraquinone dissolved in warm glacial acetic acid. The azine separates as a crystalline precipitate, m. p. 217° (Hinsberg, *loc. cit.*, p. 340).

This reaction is generally employed to establish the orientation of amino-groups in the benzene ring, as *meta-* and *para*-diamines do not condense in this way. It is also used to determine the relative positions of nitro-groups in dinitro-compounds and of nitro- and amino-groups in nitroanilines. For this purpose it is obviously necessary to reduce them to the corresponding diamine. The experimental procedure described below avoids the isolation of the diamine, which is often troublesome.

Preparation of 1 : 2-*Dimethoxyphenanthrazine.*—3 : 4-Dinitroveratrole (0·5 g.) dissolved in 10 c.c. of boiling alcohol is mixed with 5 c.c. of concentrated hydrochloric acid. An excess of zinc dust is added in one portion. When the vigorous reaction has subsided, water is added, the solution filtered, and the filtrate mixed with sodium acetate. A solution of phenanthraquinone in hot aqueous sodium bisulphite solution containing sodium acetate is then added and the mixture boiled. The azine soon separates. It is collected, washed, and purified by crystallisation from alcohol. It crystallises in long needles, m. p. 175° (T. G. H. Jones and Robinson, *J.*, 1917, **111**, 912).

Preparation of 2 : 3-*Diphenyl-*6-n-*butylquinoxaline.*—3-Nitro-4-amino-*n*-butylbenzene (1·4 g.) is reduced by the gradual addition of zinc dust to a boiling solution in an excess of 50% acetic acid. A solution of benzil (1·5 g.) in warm sodium bisulphite solution is then added and the mixture boiled for 5 minutes. A reddish-brown oil separates. It is collected after cooling and crystallised from warm methyl alcohol—small yellow needles, m. p. 82° (Reilly and Hickinbottom, *J.*, 1920, **117**, 118).

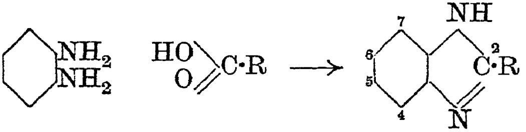
Instead of benzil or phenanthraquinone, other 1 : 2-diketones may be used. Indeed, the reaction is used also for the recognition of 1 : 2-diketones. Among the dicarbonyl compounds which have been used in this condensation are β-naphthaquinone and isatin. Glyoxal also condenses readily with *ortho*-diamines. The products, however, are generally more basic than those derived from diketones containing aryl groupings.

Preparation of Quinoxaline.—A slight excess of finely-powdered glyoxal bisulphite compound is added to an aqueous solution of *o*-phenylenediamine maintained at 50—60°. The mixture is stirred till all the bisulphite compound has dissolved. An excess of alkali is then added. The quinoxaline which separates is taken up in ether, dried with potassium hydroxide, and distilled —b. p. 220—223°, m. p. 27°. It yields well-defined salts with many mineral acids (Hinsberg, *loc. cit.*, p. 334).

Ethylenediamine also condenses with benzil and phenanthraquinone to give compounds which are analogous to those derived from aromatic diamines (Mason, *Ber.*, 1886, **19**, 112; 1887, **20**, 267). There appears to be no record of aliphatic 1 : 3- or 1 : 4-diamines condensing in this way.

Condensations of aromatic *ortho*-diamines, which are similar in form to those with 1 : 2-diketones, are also given by α-keto-acids (Hinsberg, *Annalen*, 1887, **237**, 347).

Formation of Iminazoles (Anhydro-Bases).—When aromatic *ortho*-diamines are heated under reflux with acetic or formic acids or their homologues, the product is a benziminazole of the general formula (III).



(III.)

(Ladenburg, *Ber.*, 1875, **8**, 677; 1877, **10**, 1123; Wundt, *ibid.*, 1878, **11**, 826). These substances are bases, and are generally recognised by their sparingly soluble picrates. The anhydro-bases are also formed by warming the monoacetyl derivatives of *ortho*-diamines, or by the vigorous reduction of an acetyl derivative of an *o*-nitroamine (Hübner and Rudolph, *Ber.*, 1875, **8**, 472; Hübner, *Annalen*, 1881, **208**, 278; Bamberger and Lorenzen, *ibid.*, 1893, **273**, 272).

Preparation of Benziminazole.—*o*-Phenylenediamine is heated under reflux for 1 hour with a moderate excess of anhydrous formic acid. The excess of acid is then removed by distillation, and the residue, which solidifies on cooling, is crystallised from alcohol or water, m. p. 167° (Wundt, *loc. cit.*; Pauly and Gundermann, *Ber.*, 1908, **41**, 4011).

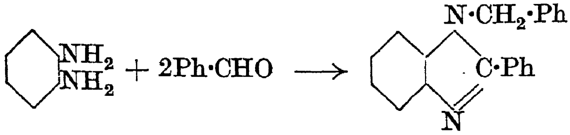
Preparation of 5-Methylbenziminazole.—3 : 4-Toluylenediamine is heated under reflux for 8 hours with four times its weight of formic acid (*d* 1·2). The dark solution is then treated with an excess of sodium carbonate, and the oil which separates is taken up in ether. After drying the ethereal solution and evaporating the solvent, the anhydro-base remains, m. p. 94° (O. Fischer, *Ber.*, 1893, **26**, 195).

By substituting acetic or propionic acid for formic acid in these preparations, the corresponding 2-alkylbenziminazoles are formed.

Although the anhydro-bases result by heating aromatic diamines with a fatty acid, the normal diacyl derivatives are formed by the action of the acid anhydrides. Dibenzoyl derivatives are formed by the application of the Schotten–Baumann method of acylation. The diacyl derivatives in general pass more or less readily into the anhydro-bases on keeping in the fused state (Hartmann, *Ber.*, 1890, **23**, 1049; Bistrzycki and Ulffers, *ibid.*, p. 1876). When this method is unsatisfactory, the anhydro-base may be obtained by heating in a stream of hydrogen chloride or by heating with concentrated hydrochloric acid at 200° (compare Walther and v. Pulawski, *J. pr. Chem.*, 1899, [ii], **59**, 249).

Anhydro-bases can also be obtained from diacyl derivatives of aliphatic diamines by distillation or by heating in a stream of hydrogen chloride. A more general method is to distil the hydrochloride with the sodium salt of a lower fatty acid (Hofmann, *Ber.*, 1888, **21**, 2332; Ladenburg, *ibid.*, 1894, **27**, 2952; Klingelstein, *ibid.*, 1895, **28**, 1173; Baumann, *ibid.*, p. 1176; Morgan and Hickinbottom, *J.S.C.I.*, 1924, **43**, 310T). The formation of anhydro-bases is, however, not confined to aliphatic 1 : 2-diamines. Trimethylenediamine dihydrochloride and tetramethylene dihydrochloride also furnish anhydro-bases on distillation with sodium acetate (Harries and Haga, *Ber.*, 1899, **32**, 1191; Haga and Majima, *ibid.*, 1903, **36**, 333).

Reaction with Aldehydes : Formation of Aldehydines.—These substances are formed when salts of aromatic *ortho*-diamines are treated with aldehydes (Ladenburg, *Ber.*, 1878, **11**, 590, 600, 1648, 1653; Hinsberg, *ibid.*, 1886, **19**, 2025; 1887, **20**, 1585; Hinsberg and Funcke, *ibid.*, 1893, **26**, 3092; 1894, **27**, 2187).



Preparation of 5-Methyl-1-benzyl-2-phenylbenziminazole.—A solution of 5 g. of *o*-toluylenediamine hydrochloride in 100 c.c. of water is shaken with 5 g. of benzaldehyde. After keeping for several hours, the amorphous mass has become crystalline. It is collected, washed with ether, and then dissolved in water containing a little hydrochloric acid. After filtering, an excess of concentrated hydrochloric acid is added. The hydrochloride of the aldehydine is precipitated. The free base has m. p. 195—196° (Ladenburg, *loc. cit.*, p. 1649).

This compound is also prepared, although in poorer yield, by heating the aldehyde and diamine at 140° for 18 hours.

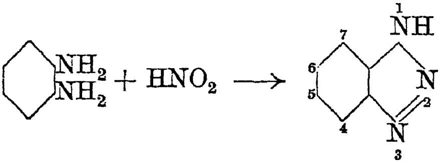
Preparation of 1-Ethyl-2-methylbenziminazole.—A solution of *o*-phenylenediamine (10 g.) in dilute acetic acid is mixed with acetaldehyde (9 g.) and then evaporated on a water-bath. The residue is treated with alkali, the base taken up in ether and purified by crystallisation of its sparingly soluble hydroiodide, $C_{10}H_{12}N_2,HI,2H_2O$, which separates from water as needles. The base liberated from its salt by the addition of excess of alkali is a liquid, b. p. 257° 60 mm.

Some 2-methylbenziminazole is also formed in this preparation. It can be isolated by taking advantage of its comparatively low solubility in ether when the crude reaction product is rendered alkaline. It is purified by crystallisation of its tartrate. The free base melts at 175 (Hinsberg and Funcke, *Ber.*, 1894, **27**, 2187).

It appears that normal bisazomethines can be obtained from the reaction of benzaldehyde with *o*-diamines in alcohol. These pass into aldehydine more or less readily on warming with dilute hydrochloric acid or acetic acid (Hinsberg and Koller, *Ber.*, 1896, **29**, 1497; Hinsberg and Funcke, *loc. cit.*).

The aliphatic 1 : 2-diamines, in contrast to the aromatic diamines, do not appear to yield aldehydines; bisazomethines are formed instead (Mason, *Ber.*, 1887, **20**, 276; Strache, *ibid.*, 1888, **21**, 2358).

Other Reactions of 1 : 2-Diamines.—Aromatic *ortho*-diamines react with nitrous acid in dilute aqueous solution containing some acid to yield azimides (V) (Ladenburg, *Ber.*, 1876, **9**, 219, 1524).



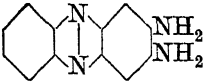
(V.)

Preparation of 5-Methylazimidobenzene.—A dilute aqueous solution of sodium nitrite (1 mol. proportion) is gradually added to a dilute aqueous solution of 3 : 4-toluylenediamine hydrochloride cooled to 0°. After a portion of the nitrite has been added, the brownish precipitate which separates is filtered off. The azimide separates from the filtrate as a white crystalline precipitate, m. p. 83°, on adding the remainder of the nitrite (Nölting and Abt, *Ber.*, 1887, **20**, 3001).

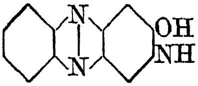
Preparation of 4-Nitroazimidobenzene.—The calculated amount of sodium nitrite in aqueous solution is added to a solution of 3-nitro-*o*-phenylenediamine in very dilute hydrochloric acid cooled to 0°. The azimide separates as a dark yellow flocculent precipitate, which is collected and washed with water. It is crystallised from hot water—pale yellow needles, m. p. 211° (Zinke, *Annalen*, 1900, **311**, 290).

Oxidation of aromatic *ortho*-diamines in concentrated aqueous solution with ferric chloride leads to the formation of a diaminophenazine (VI) (Griess, *J. pr. Chem.*, 1871, [ii], **3**, 143; O. Fischer and Hepp, *Ber.*, 1889, **22**, 356). Should there be excess of free hydrochloric acid present, this product may be contaminated with a hydroxyaminophenazine (VII) (Ullmann and Mauthner, *Ber.*, 1902, **35**, 4302).

If silver oxide or lead peroxide be used as the oxidising agent acting on a dry ethereal solution of *o*-phenylenediamine, *o*-quinone-di-imine (VIII) appears to be formed. On warming or treating with dilute hydrochloric acid, diaminophenazine results with some 2 : 2′-diaminoazobenzene (IX) (Willstätter and Pfannenstiel, *Ber.*, 1905, **38**, 2348).



(VI.)



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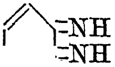
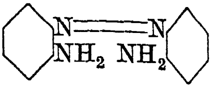


(VIII.)



(IX.)

Phosgene reacts with some *o*-diamines with the formation of cyclic ureas (Hartmann, *Ber.*, 1890, **23**, 1046), while the analogous cyclic thioureas result by heating salts of the diamines with ammonium thiocyanide or by heating the product of reaction with mustard oils (Lellmann, *Annalen*, 1885, **228**, 249).

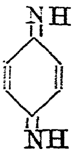
(b) 1 : 3-*Aromatic Diamines.*—These diamines yield normal diacyl derivatives on heating with fatty acids; bisazomethines are formed by reaction with aldehydes. Further, the *meta*-diamines do not yield azines by condensation with 1 : 2-diketones. These diamines are therefore sharply distinguished from *ortho*-diamines.

If it is attempted to diazotise *m*-phenylenediamines under conditions which succeed with monoamines, a more or less intense brownish coloration results. Under suitable conditions the reaction is very sensitive, and has been used for the estimation of small amounts of nitrite (Griess, *Ber.*, 1878, **11**, 624; Preusse and Tiemann, *ibid.*, p. 627). 2 : 4-Diaminotoluene and many other diamines behave similarly, exceptions being those *m*-diamines with a substituent which is *ortho* to both amino-groups (Cain, *Chemistry of the Diazo-Compounds*, 1908, p. 20). These yield normal bisdiazo-compounds. The formation of a bisdiazo-compound from *m*-phenylenediamine requires special conditions—an excess of nitrous acid and of concentrated hydrochloric acid (Griess, *Ber.*, 1886, **19**, 317; Täuber and Walder, *ibid.*, 1897, **30**, 2901). Even these conditions fail with some diamines (compare Lees and Thorpe, *J.*, 1907, **91**, 1288).

The reactions of aliphatic 1 : 3- and other diamines are discussed on p. 299.

(c) 1 : 4-*Aromatic diamines* resemble the *meta*-diamines in not yielding anhydro-bases or azines. Diazotisation of *p*-diamines takes place more or less readily. Usually a mixture of mono- and bisdiazo-compounds results. The behaviour of *p*-diamines on oxidation is characteristic. If the oxidation is effected by manganese dioxide and sulphuric acid or with dichromate and sulphuric acid, the product is a *p*-quinone (Hofmann, *Proc. Roy. Soc.*, 1836, **12**, 639; Meldola and R. E. Evans, *Proc.*, 1889, **5**, 115; Willstätter and Dorogi, *Ber.*, 1909, **42**, 2166; compare Nef, *ibid.*, 1888, **18**, 2806). Oxidation under milder conditions generally results in the formation of quinonoid compounds. Thus *p*-phenylenediamine in dry ethereal solution yields *p*-benzoquinonedi-imine (X) by treatment with dry silver oxide (Willstätter and Pfannenstiel, *Ber.*, 1904, **37**, 4605). When oxidation is effected in aqueous ammonia solution by ferricyanide or by molecular oxygen, a complex quinonoid compound—"Bandrowski's base (XI)"—is formed (*Ber.*, 1894, 27, 480; Willstätter and E. Mayer, *ibid.*, 1904, **37**, 1494).

The tendency to yield quinonoid compounds on oxidation is doubtless responsible for the various colour reactions which have been described for *p*-diamines. Thus the addition of ferric chloride to a solution of *p*-phenylenediamine mixed with a little aniline produces an intense green-blue coloration owing to the formation of indamine (XII). The same product is formed by adding dichromate to equimolecular proportions of *p*-phenylenediamine in dilute acetic acid solution. If the oxidation is effected in presence of 2 molecular proportions of aniline, safranine (XIII) is formed.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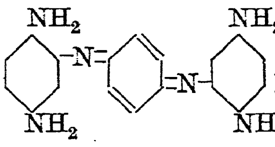
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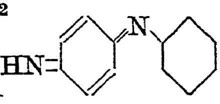
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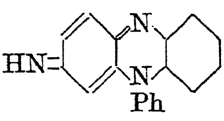
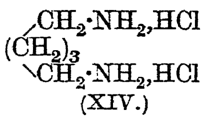
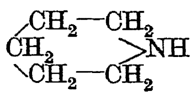

(XIII.)

(d) *Formation of Cyclic Compounds from Aliphatic Diamines.*—The formation of anhydro-bases has already been referred to (p. 296). Another type of reaction is the production of cyclic imines when salts of the diamine are heated. This occurs very readily with 1 : 4- and 1 : 5-diamines. Thus pentamethylenediamine dihydrochloride (XIV) yields piperidine (XV) on heating, while tetramethylenediamine dihydrochloride furnishes pyrrolidine (XVI) (Ladenburg, *Ber.*, 1885, **18**, 3100; 1887, **20**, 442). If the amino-groups are more remote from each other, cyclisation occurs, but the products appear to be anomalous. Thus octamethylenediamine dihydrochloride



$$(CH_2)_3\begin{cases}CH_2\cdot NH_2,HCl\\ CH_2\cdot NH_2,HCl\end{cases}$$

(XIV.)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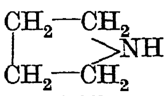
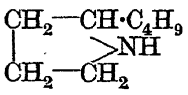
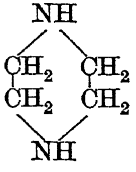
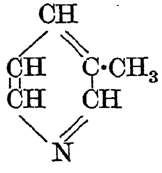

(XVI.)


(XVII.)


(XVIII.)


(XIX.)

furnishes *n*-butylpyrrolidine (XVII) (Blaise and Houillon, *Compt. rend.*, 1906, **142**, 1541; **143**, 361). These authors suggest that decamethylene imine (Krafft, *Ber.*, 1906, **39**, 2193) and heptamethylene imine (v. Braun and Müller, *Ber.*, 1906, **39**, 4110), which have been prepared from the corresponding diamines, may also be substituted pyrrolidines.

Ethylenediamine dihydrochloride, on the other hand, yields piperazine (XVIII) as a product of distillation (Ladenburg and Abel, *Ber.*, 1888, **21**, 758), while trimethylenediamine dihydrochloride furnishes a mixture of β-methylpyridine (XIX) and trimethylene imine (Ladenburg and Sieber, *Ber.*, 1890, **23**, 2727).

(3) *Quaternary Ammonium Salts.*

The halide salts are derived by the addition of alkyl halides to tertiary amines, and are represented by the general formula $RR'R''R'''N{\cdot}I$. They are salts derived from the corresponding quaternary ammonium hydroxides, which, in general, are strong bases readily soluble in water, turning red-litmus blue and combining directly with carbon dioxide. Determinations of the strength of the tetra-alkyl ammonium hydroxides show that they are approximately as strong as the caustic alkalis (J. Walker and Johnston, *J.*, 1905, **87**, 961; Bredig, *Z. phys. Chem.*, 1894, **13**, 300).

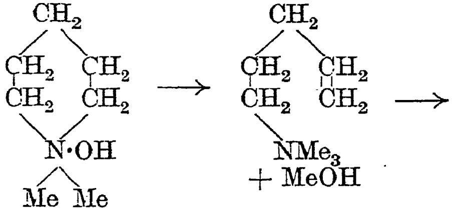
Aqueous solutions of the quaternary ammonium hydroxides are obtained by treatment of the halides in aqueous solution with an excess of silver oxide, and subsequently removing the suspended silver halide and excess of silver oxide. In general, treatment of the quaternary ammonium salts with caustic alkalis is not suitable for the preparation of the quaternary ammonium hydroxides. If, however, conditions are so arranged that one of the products is precipitated, the free ammonium hydroxide can be obtained. Thus Walker and Johnston (*loc. cit.*, p. 956) prepare tetramethylammonium hydroxide by interaction of the chloride with caustic potash in absolute methyl alcohol. Crichton (J., 1907, **91**, 1793) has employed the same method for the preparation of tetraethyl- and of tetrapropyl-ammonium hydroxides. Aqueous solutions of the ammonium hydroxides can also be obtained by treating the quaternary ammonium sulphate with the calculated amount of baryta solution.

Quaternary ammonium hydroxides, in general, decompose on heating with the formation of tertiary amines. Thus tetramethylammonium hydroxide yields methyl alcohol and trimethylamine. Alkyl groups other than methyl are split off as olefin.

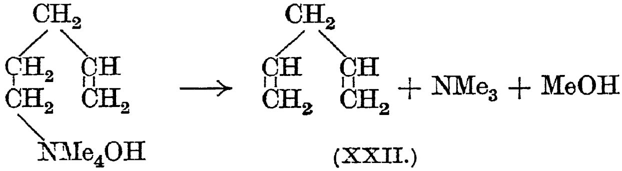
Dimethylpyrrolidinium hydroxide under similar treatment yields butadiene. This method has frequently been applied to the degradation of cyclic nitrogenous compounds. The following papers may be consulted: Willstätter, *Annalen*, 1901, **317**, 230; Willstätter and Waser, *Ber.*, 1911, **44**, 3455.

It must be noted, however, that all cyclic quaternary ammonium hydroxides do not decompose to open the ring. Thus methyl kairolinium hydriodide yields methyl alcohol and kairoline (methyltetrahydroquinoline) on heating (Feer and Koenigs, *Ber.*, 1885, **18**, 2393), while ethylmethylpiperidinium hydroxide and *n*-propylmethylpiperidinium hydroxide furnish alkyl piperidines as the principal products on heating (Hofmann, *Ber.*, 1881, **14**, 660; v. Braun, *Ber.*, 1909, **42**, 2532). On the other hand, if benzylpiperidine or *iso*amylpiperidine is subjected to exhaustive methylation, the ring is opened (Schotten, *Ber.*, 1882, **15**, 421).

The quaternary ammonium salts also decompose on heating with the formation of a tertiary amine. Thus tetramethylammonium chloride yields methyl chloride and trimethylamine; the acetate furnishes methyl acetate; the benzoate methyl benzoate and trimethylamine. Higher alkyl groups are usually split off as olefins. This method of degrading quaternary ammonium compounds does not appear to have been so extensively used as the decomposition of the hydroxide (Hofmann, *Annalen*, 1851, **78**, 268; Lawson and Collie, *J.*, 1888, **53**, 624; Meyer and Lecco, *Annalen*, 1876, **180**, 184; Lossen, *ibid.*, 1876, **181**, 377).



(XX.) (XXI.)



(XXII.)

$$(C_2H_5)_4N{\cdot}OH \longrightarrow (C_2H_5)_3N + C_2H_4 + H_2O$$

Quaternary ammonium salts with dissimilar alkyl groups can break down in more than one way to furnish a mixture of products. While it is not possible in every case to predict with certainty the direction in which decomposition will principally occur, it appears that the methyl group is less readily eliminated than other alkyl groups. v. Braun (*Annalen*, 1911, **382**, 5) gives the following order of ease of elimination: allyl > benzyl > ethyl > propyl > *iso*amyl > methyl.

More recently, Ingold and his collaborators have studied the effects of constitution on the direction of decomposition of quaternary ammonium hydroxides of the type $R{\cdot}NMe_3{\cdot}OH$. Their results are of importance in that they appear to confirm the theoretical speculations of Ingold on the mechanism of the reaction (Hanhart and Ingold, *J.*, 1927, 997; Ingold and Vass, *ibid.*, 1928, 3125; Ingold and

Jessop, *ibid.*, 1929, 2357; Hughes and Ingold, *ibid.*, 1933, 69, 523; Hughes, Ingold, and Patel, *ibid.*, p. 526; Hey and Ingold, *ibid.*, p. 66; Ingold and Patel, *ibid.*, p. 68).

The decomposition of the ammonium hydroxides is of considerable interest when applied to the saturated cyclic quaternary ammonium hydroxides, for under suitable conditions it leads to the elimination of the nitrogen and the opening of the ring. Thus piperidinium dimethyl hydroxide (XX) yields (XXI) on heating. By combining this tertiary amine with methyl iodide and then heating the ammonium hydroxide derived from it, trimethylamine and (XXII) are formed (Hofmann, *Ber.*, 1881, **14**, 659; Ladenburg, *ibid.*, 1883, **16**, 2058). This process is often designated "exhaustive methylation."

TABLE XIV.

Aliphatic Primary Amines.

	B. p.	M. p.	Acetyl. M. p.	Benzoyl. M. p.	*p*-Toluene sulphonyl. M. p.	Benzene sulphonyl. M. p.	Picrate. M. p.	Alkyl thio-phenyl urea. M. p.	
Methylamine	—6°	—	[206°]	80°	77°	—	215°	—	
Ethylamine	18	—	[205]	69	62	—	168	99°	
*iso*Propylamine	31	—	—	—	—	—	—	—	
n-Propylamine	49	—	[222]	85	52	—	135	63	
Allylamine	58	—	[109/ 12 mm.]	[173/ 14 mm.]	—	39°	140	100	
sec.-Butylamine	63	—	—	—	—	—	—	—	
*iso*Butylamine	68	—	—	57	78	—	—	—	
n-Butylamine	78	—	—	—	—	—	—	—	
*iso*Amylamine	95	—	—	—	65	—	—	102	
Ethylenediamine	116	—	172	249	160	168	233	—	
Ethylenediamine hydrate	118	10°	—	—	—	—	—	—	
1 : 2-Diaminopropane	120	—	139	192	103	—	—	—	
1 : 3-Diaminopropane	136	—	126	147	148	96	—	—	
1 : 4-Diaminobutane	160	—	—	—	—	—	—	—	
1 : 5-Diaminopentane	178	—	—	—	—	119	—	—	
β-Hydroxyethylamine	167	—	—	—	—	—	160	—	
Benzylamine	184	—	61	106	—	—	—	—	Benzyl urea, m. p. 147°; reaction with PhNCO → m. p. 168°.
α-Phenylethylamine	185	—	57	120	—	—	141	—	
β-Phenylethylamine	196	—	42, 52*	114	—	—	167	135	β-Phenylethyl urea, m. p. 112°.

* Both values given in literature.

[] in a column headed B. p. indicate that the substance is solid. The figures within the brackets give the m. p. Conversely, in a column headed M. p. the figures within the brackets give the b. p. of a liquid.

TABLE XV.

Primary Aromatic Amines.

	B. p.	M. p.	Formyl. M. p.	Acetyl. M. p.	Benzoyl. M. p.	Benzene sulphonyl. M. p.	*p*-Toluene sulphonyl. M. p.	2 : 4-Dinitro phenyl.(*a*) M. p.	$\begin{matrix}\mathrm{RNH}\\\mathrm{H_2N}\end{matrix}>\mathrm{CO}$ (*b*) M. p.	$\begin{matrix}\mathrm{RNH}\\\mathrm{PhNH}\end{matrix}>\mathrm{CO}$ (*c*) M. p.	$\begin{matrix}\mathrm{RNH}\\\mathrm{PhNH}\end{matrix}>\mathrm{CS}$ (*d*) M. p.	
Aniline	184°	—	47°	114°	161°	105°	103°	—	147°	236°	154°	*m*-Nitrobenzene sulphonyl, m. p. 126°; benzal deriv., m. p. 54°.
o-Toluidine	199	—	59	109	144	123	108	126°	190	196	—	*m*-Nitrobenzene sulphonyl, m. p. 164°; 3-nitrobenzal deriv., m. p. 78°; 2 : 4-dinitrobenzal deriv., m. p. 153°.
m-Toluidine	199	—	—	66	125	95	114	160	142	173	91	4-Chlorobenzal deriv., m. p. 32°.
p-Toluidine	200	43°	53	145	158	121	118	136	181	212	142	*m*-Nitrobenzene sulphonyl, m. p. 132°; 3-nitrobenzal deriv., m. p. 96°; 4-nitrobenzal deriv., m. p. 124°.
o-Chloraniline	208	—	—	88	99	120	—	—	—	—	—	
2-Amino-*p*-xylene	213	15	112	139	140	139	119	—	—	—	—	Benzal deriv., m. p. 101°; salicylal deriv., m. p. 108°.
4-Amino-*m*-xylene	215	—	114	128	192	129	—	—	207	243	126	Salicylal deriv., m. p. 30°.
2-Amino-*m*-xylene	216	—	—	177	127	—	—	—	—	—	—	
o-Aminodimethylaniline	217	—	—	—	—	—	—	—	—	—	—	Difficultly sol. in water. $FeCl_3 \rightarrow$ deep red in alc. Picrate, m. p. 138° dec.
o-Anisidine	218	5	—	84	—	89	127	151	—	—	—	
5-Amino-*m*-xylene	221	—	77	144	—	—	—	—	—	—	—	
3-Amino-*o*-xylene	223	—	—	134	—	—	—	—	—	—	—	
m-Chloraniline	236	—	—	72	118	121	—	—	—	—	—	
4-Amino-*o*-xylene	224	48	—	99	—	—	154	—	—	—	—	Salicylal deriv., m. p. 76°.
4-Amino-*iso*propylbenzene	225	—	—	102	162	—	—	—	—	—	—	
o-Phenetidine	229	—	—	79	—	—	164	—	—	—	—	
Mesidine	229	—	176	216	204	—	—	—	—	—	—	
ψ-Cumidine	234	63	121	161	167	137	—	—	237	212	—	Cinnamal deriv., m. p. 105°.
3-Chloro-4-aminotoluene	223	7	—	113	137	—	—	—	—	—	—	
2-Amino-*p*-cymene	241	—	—	71	102	—	—	—	—	—	—	
p-Anisidine	243	57	—	127	153	95	114	141	—	—	—	
o-Aminomethylaniline	245	—	—	—	—	—	—	—	—	—	—	
*iso*Duridine	255	24	183	211	—	—	—	—	—	—	—	
Methyl ester of anthranilic acid	255	25	—	101	—	107	—	—	—	—	—	Orange blossom odour.
p-Phenetidine	254	—	—	—	173	—	—	—	—	—	—	
Ethyl ester of anthranilic acid	267	13	—	61	98	92	—	—	—	—	—	Feeble odour.
Ethyl ester of *m*-aminobenzoic acid	294	—	—	—	114	—	—	—	—	—	—	
ar-Tetrahydro-*α*-naphthylamine	275	—	—	158	—	—	—	—	—	—	—	
m-Bromaniline	—	17	—	88	120	—	—	—	165	—	—	
m-Iodoaniline	—	30	—	119	—	—	—	—	—	—	—	
3-Bromo-4-aminotoluene	240	26	—	118	149	—	—	—	—	—	—	

3-Bromo-4-aminotoluene	240	26	—	118	149	—	—	—	—	—	—

(*a*) Product of reaction with 2 : 4-dinitrochlorobenzene or 2 : 4-dinitrobromobenzene, see p. 271.
(*b*) Product of action of KCNO on amine salt or on sol. of amine in acetic acid, see p. 266.
(*c*) Product of action of phenylcarbimide on amine, see p. 266. (*d*) Product of action of phenylmustard oil on amine, see p. 267

5-Chloro-2-aminotoluene	241	20	—	140	—	—	—	—	—	—	—	
o-Bromaniline	229	31	87	99	116	—	—	—	202	—	—	
p-Aminomethylaniline	258	36	—	—	[165]	—	—	—	—	—	—	FeCl$_3$ on aq. sol. hydrochloride → intense red.
ar-Tetrahydro-*β*-naphthylamine	275	38	—	107	—	—	—	—	—	—	—	
5-Chloro-4-amino-*m*-xylene	—	40	—	—	148	—	—	—	—	—	—	
p-Aminodimethylaniline	258	41	—	130	—	—	—	—	—	—	—	
2 : 4′-Diaminodiphenyl	363	45	—	202	278	—	—	—	—	—	—	
5-Bromo-5-amino-*m*-xylene	—	47	—	197	—	—	—	—	—	—	—	
2 : 5-Dichloraniline	—	50	—	132	120	—	—	—	—	—	—	
3 : 5-Dibromo-2-aminotoluene	—	50	—	205	—	—	—	—	—	—	—	
α-Naphthylamine	—	50	137	160	161	161	157	190	214	223	157	3-Nitrobenzal deriv., m. p. 102°; 2 : 4-dinitrobenzal deriv., m. p. 203°.
3 : 5-Dichloro-2-aminotoluene	—	50	—	186	—	—	—	—	—	—	—	
3 : 5-Dichloro-4-aminotoluene	—	60	—	—	—	—	—	—	—	—	—	
2 : 3-Diaminotoluene	255	61	—	—	—	—	—	—	—	—	—	
5-Bromo-2-aminotoluene	—	59	—	156	—	—	—	—	—	—	—	
o-Iodoaniline	—	60	—	110	—	—	—	—	—	—	—	
2 : 4-Dichloraniline	245	63	153	146	115	128	—	—	—	—	—	
m-Phenylenediamine	283	63	—	[190]	240	—	172	—	—	—	—	Very easily sol. in water.
p-Iodoaniline	—	64	109	181	210	—	—	—	—	—	—	
p-Bromaniline	—	64	—	166	202	134	—	—	207	—	158	
2 : 5-Diaminotoluene	—	64	—	[220]	—	—	—	—	—	—	—	Easily sol. in water. Oxidised → *p*-toluquinone.
1 : 8-Diaminonaphthalene	—	67	—	—	—	—	—	—	—	—	—	FeCl$_3$ on base → brown ppt. Heat with formic acid → perimidine, m. p. 222°; with acetic acid → *μ*-methyl perimidine, m. p. 210° dec.
p-Chloraniline	—	70	—	179	192	121	—	—	212	—	152	
o-Nitraniline	—	72	—	93	98	104	—	—	—	—	—	
2-Nitro-4-aminotoluene	—	72	—	93	172	160	—	—	—	—	—	
4-Nitromesidine	—	75	—	191	169	163	—	—	—	—	—	
4-Aminodiphenylamine (anhydr.)	—	75	—	158	[203]	—	—	190	—	—	—	FeCl$_3$ on aq. sol. of hydrochloride → red → green; CrO$_3$ and H$_2$SO$_4$ → *p*-benzoquinone.
5-Nitro-4-amino-*m*-xylene	—	76	—	173	185	—	—	—	—	—	—	
3 : 5-Dibromo-4-aminotoluene	—	78	—	183	—	—	—	—	—	—	—	
2 : 4 : 6-Trichloraniline	262	78	180	204	—	—	—	—	—	—	—	
2 : 4-Dibromaniline	—	79	—	146	134	—	—	—	—	—	—	
2-Aminodiphenylamine	—	80	—	—	—	—	—	—	—	—	—	
6-Chloro-3-aminotoluene	241	83	—	91	—	—	—	—	—	—	—	
2 : 6-Dibromaniline	—	83	—	210	—	—	—	—	—	—	—	
3 : 4-Diaminotoluene	265	89	—	—	—	—	—	—	—	—	—	Fairly easily sol. in cold water. Diphenyltoluquinoxaline, m. p. 111°; methyltoliminazole, m. p. 203°.
Ethyl ester of *p*-aminobenzoic acid	—	89	—	110	148	—	—	—	—	—	—	
6-Nitro-2-aminotoluene	—	91	—	158	167	—	—	—	—	—	—	
4-Chloro-2 : 6-dibromaniline	301	93	—	226	194	—	—	—	—	—	—	
4 : 4′-Diaminodiphenylmethane	—	94	—	228	—	—	—	—	—	—	—	
6-Chloro-2 : 4-dibromaniline	—	95	—	227	192	—	—	—	—	—	—	

TABLE XV—*continued.*
Primary Aromatic Amines.

	B. p.	M. p.	Formyl. M. p.	Acetyl. M. p.	Benzoyl. M. p.	Benzene sulphonyl. M. p.	*p*-Toluene sulphonyl. M. p.	2 : 4-Dinitrophenyl.(*a*) M. p.	RNH·CO·NH$_2$.(*b*) M. p.	RNH·CO·NHPh.(*c*) M. p.	RNH·CS·NHPh.(*d*) M. p.	
1 : 2-Diaminonaphthalene	—	95	—	[234]	[201]	—	—	—	—	—	—	FeCl$_3$ on hydrochloride ⟶ green.
2 : 4-Di-iodoaniline	—	96	—	—	181		—	—	—	—	—	
3-Nitro-2-aminotoluene	—	97	—	158	—	—	—	—	—	—	—	
4-Chloro-α-naphthylamine	—	98	—	184	—	—	—	—	—	—	—	
8-Nitro-α-naphthylamine	—	97	—	191	—	194	—	—	—	—	—	
2 : 4-Diaminotoluene	280	99	—	[224]	[224]	192	—	—	—	—	—	Easily sol. in boiling water.
4-Nitro-2-aminotoluene	—	107	—	151	—	172	—	—	—	—	—	
o-Phenylenediamine	256	103	—	186	301	—	—	—	—	—	—	Phenanthraphenazine, m. p. 217°; 2-methylbenziminazole, m. p. 175°; FeCl$_3$ ⟶ ruby-red coloration and ppt. of diaminophenazine if not too dilute.
β-Naphthylamine	306	112	128	133	162	98	133	179	214 dec.	220	157	3-Nitrobenzal deriv., m. p. 91°; 2 : 4-dinitrobenzal deriv., m. p. 199°.
m-Nitraniline	—	115	134	154	155	136	—	—	—	—	155	3-Nitrobenzal deriv., m. p. 154°.
2 : 4 : 6-Tribromaniline	—	118	—	232	198	—	—	—	—	—	—	
3-Nitro-4-aminotoluene	—	116	—	92	143	99	100	—	—	—	—	
5-Nitro-α-naphthylamine	—	119	—	220	—	183	—	—	—	—	—	
1 : 4-Diaminonaphthalene	—	120	—	[303]	[280]	—	—	—	—	—	—	FeCl$_3$ on aq. sol. ⟶ green coloration. Conc. sol. ⟶ naphthaquinone.
6-Nitro-4-amino-*m*-xylene	—	123	—	159	200	149	—	—	—	—	—	
1-Nitro-*β*-naphthylamine	—	126	—	124	—	156	159	—	—	—	—	
Benzidine	400	127	—	317	352	235	243	—	—	—	—	
Di-*o*-toluidine	—	129	254	314	265	—	—	—	—	—	—	
5-Nitro-2-aminotoluene	—	130	—	202	—	158	174	—	—	—	—	
6-Nitro-3-aminotoluene	—	135	—	102	—		—	—	—	—	—	
p-Phenylenediamine (anhydr.)	—	140	—	303	>300	266	—	—	—	—	—	Hydrated, +2H$_2$O, m. p. 80°. Dil. acid dichromate ⟶ *p*-benzoquinone.
5-Nitro-2-amino-*p*-xylene	—	142	—	166	—	162	—	—	—	—	—	
5-Nitro-*β*-naphthylamine	—	144	—	186	182	—	—	—	—	—	—	
2-Nitro-α-naphthylamine	—	144	—	199	174	—	—	—	—	—	—	
p-Nitraniline	—	145	71	—	197	139	190	—	—	—	—	Benzal deriv., m. p. 115°.
3 : 5-Dinitro-4-aminotoluene	—	166	—	—	—	—	—	—	—	—	—	
2 : 6-Dinitro-4-aminotoluene	—	169	—	—	—	—	—	—	—	—	—	
2 : 4-Dinitraniline	—	186	—	120	220	—	—	—	—	—	—	
2 : 4 : 6-Trinitraniline	—	188	—	—	—	—	—	—	—	—	—	
4-Nitro-α-naphthylamine	—	195	—	190	224	158	185	—	—	—	—	
Dinitromesidine	—	194	—	275	—	—	—	—	—	—	—	
4 : 4′-Diaminostilbene	—	226	—	312	—	—	—	—	—	—	—	

[ ] in a column headed B. p. indicate that the substance is solid. The figures within the brackets give the m. p.

TABLE XVI.

Secondary Amines.

	B. p.	M. p.	Acetyl. M. p.	Benzoyl. M. p.	*p*-Toluene sulphonyl. M. p.	Benzene sulphonyl. M. p.	Nitrosamine. M. p.	
Dimethylamine	7°	—	[166]°	42°	79°	47°	—	
Diethylamine	56	—	[186]	—	60	42	—	
Di-*n*-propylamine	110	—	—	—	—	51	—	
Piperidine	105	—	[226]	48	—	93	—	
Diallylamine	111	—	—	—	—	—	—	
Di*iso*butylamine	140	—	—	—	—	—	—	
Piperazine	140	104°	134	191	—	282	158	
Methylaniline	194	—	101	63	95	78	—	
Ethylaniline	206	—	53	60	88	—	—	
Methyl-*o*-toluidine	207	—	56	66	—	—	—	
Methyl-*m*-toluidine	207	—	—	—	—	—		
Methyl-*p*-toluidine	208	—	83	—	—	—	53°	
*iso*Propylaniline	213	—	39	—	—	—	—	
Ethyl-*o*-toluidine	214	—	—	—	—	—	—	
Methyl-*o*-chloraniline	214	—	—	—	—	—	—	
Ethyl-*p*-toluidine	217	—	—	—	—	—	—	
4-Methylamino-*m*-xylene	221	—	—	—	—	—	—	
n-Propylaniline	222	—	48	—	—	54	—	
*iso*Butylaniline	231	—	—	—	—	—	—	
Methyl-ψ-cumidine	237	44	—	—	—	—	—	
n-Butylaniline	245	—	—	—	—	—	—	
Methyl-*p*-chloraniline	240	—	92	—	—	—	51	
Tetrahydroquinoline	251	—	[295]	75	—	67	—	
Methyl-*p*-bromaniline	260	11	—	—	—	—	88 dec.	
Di-(β-hydroxyethylamine)	270	28	—	—	—	—	—	Picrate, m. p. 101°.
Diphenylamine	302	54	100	177	141	122	66	
Methyl-α-naphthylamine	293	—	95	121	—	—	—	
Benzylaniline	299	37	58	107	—	119	58	
Methyl-β-naphthylamine	309	—	—	—	—	107	88	
Ethyl-β-naphthylamine	315	—	49	—	—	—	56	
Dibenzylamine	268/250 mm.	—	—	—	—	68	61	
Methyltribromaniline	—	39	101	—	—	—	—	
Ethyl-*o*-nitraniline	—	60	—	—	—	—	—	
2-Nitro-4-methylaminotoluene	—	45	128	—	—	—	55	
3-Nitro-4-ethylaminotoluene	—	59	liq.	—	127	—	—	
Phenyl-α-naphthylamine	—	60	115	152	—	—	—	
Methyl-*m*-nitraniline	—	66	95	156	—	83	69	
p-Tolyl-α-naphthylamine	—	79	124	140	—	—	—	
3-Nitro-4-methylaminotoluene	—	84	64	—	—	—	—	
Ethyl-*p*-nitraniline	—	96	118	98	107	—	119	
p-Tolyl-β-naphthylamine	—	103	85	139	—	—	—	
Phenyl-β-naphthylamine	—	108	93	148	—	—	93	
Ethyl-2 : 4-dinitraniline	—	113	—	—	—	—	52	
Methyl-*p*-nitraniline	—	151	152	111	—	121	101	
Methyl-2 : 4-dinitraniline	—	176	—	—	—	—	85	

[ ] in a column headed B. p. indicate that the substance is solid. The figures within the brackets give the m. p.

Conversely, in a column headed M. p. the figures within the brackets give the b. p. of a liquid.

TABLE XVII.

Tertiary Amines.

	B. p.	M. p.	Picrate. M. p.	
Trimethylamine	—	—	215°	
Triethylamine	89°	—	173	
Pyridine	115	—	167	Methiodide, m. p. 117°; metho-*p*-toluene sulphonate, m. p. 139°.
Tripropylamine	110	—	75	
a-Picoline	129	—	169	
Tri*iso*butylamine	184	—	—	
Dimethyl-*o*-toluidine	185	—	—	
Dimethylaniline	193	—	163	*p*-Nitroso-deriv., m. p. 86°; metho-*p*-toluene sulphonate, m. p. 161°.
Dimethyl-*m*-xylidine	202	—	—	
Methyl ethylaniline	206	—	134	*p*-Nitroso-deriv., m. p. 67°.
Dimethyl-*o*-chloraniline	207	—	—	
Tri-*n*-butylamine	211	—	—	Benzyl chloride → m. p. 185°.
Dimethyl-*p*-toluidine	211	—	—	Benzyl chloride → m. p. 171°; metho-*p*-toluene sulphonate, m.p. 85°.
Dimethylmesidine	213	—	—	
Dimethyl-*m*-toluidine	215	—	—	
Diethylaniline	216	—	142	*p*-Nitroso-deriv., m. p. 84°; benzyl chloride → m. p. 104°.
Dimethyl-*ψ*-cumidine	220	—	—	
Dimethyl-*p*-chloraniline	230	—	—	
Quinoline	238	—	203	Dichromate, m. p. 165°; metho-iodide, m. p. 172°; metho-*p*-toluene sulphonate, m. p. 125°.
*iso*Quinoline	240	24°	222	Methiodide, m. p. 159°; metho-*p*-toluene sulphonate, m. p. 163°.
Quinaldine	240	—	191	Mercurichloride, m. p. 165°; di-chromate, m. p. 110°; metho-*p*-toluene sulphonate, m. p. 161°.
Dimethyl-*p*-bromaniline	265	—	—	
Dimethyl-*a*-naphthylamine	272	—	—	
Ethyl benzylaniline	299	—	111	*p*-Nitroso-deriv., m. p. 62°.
Dimethyl-2 : 4 : 6-tribromaniline	301	—	—	
Dimethyl-*β*-naphthylamine	305	—	—	
Dimethyl-*m*-nitraniline	—	60	—	
Dibenzylaniline	—	70	131	*p*-Nitroso-deriv., m. p. 91°.
Diethyl-2 : 4-dinitraniline	—	80	—	
Dimethyl-2 : 4-dinitraniline	—	87	—	

Note.—For details of the preparation of metho-*p*-toluene sulphonate, see p. 272.

TABLE XVIII.

Aminophenols.

	M. p.	B. p.	Sol. in water.	
m-Hydroxyethylaniline .	62°	176°/ 12 mm.		
p-Hydroxydiphenylamine .	70	215°/ 12 mm.	Difficultly sol.	Easily sol. in dil. acids and alkalis.
m-Hydroxydiethylaniline .	78	276		4-Nitroso-3-hydroxydiethylaniline, m. p. 84°.
m-Hydroxydimethylaniline	85	266	Difficultly sol.	4-Nitroso-3-hydroxydimethylaniline, m. p. 169°.
p-Hydroxymethylaniline .	86	—		
o-Hydroxymethylaniline .	87	—		
m-Aminophenol . .	122	—	Fairly sol. 1 : 59 at 0°.	Monoacetyl deriv., m. p. 148°.
o-Aminophenol . .	173	—		
p-Aminophenol . .	185 dec.	—		Alkaline sol. → violet coloration in air; $FeCl_3$ → violet coloration.
4-Amino-α-naphthol . .	—	—		Moist solid → blue in air; ammoniacal sol. → green → yellow in air; $FeCl_3$ or dil. CrO_3 → α-naphthaquinone. Mono-acetyl deriv., m. p. 187°; monobenzoyl deriv., m. p. 228°; 3-nitrobenzal deriv., m. p. 184°; 4-nitrobenzal deriv., m. p. 171°.
1-Amino-β-naphthol . .	—	—	Difficultly sol.	$FeCl_3$ or dil. acid CrO_3 → 1 : 2-naphthaquinone. Picrate, m. p. 110°; 3-nitrobenzal deriv., m. p. 105°; 4-nitrobenzal deriv., m. p. 174°.

	M. p.	Benzoyl. M. p.	β-Naphthalene sulphonyl. M. p.	Phenyl *iso*cyanate.(*a*) M. p.	α-Naphthyl *iso*cyanate.(*a*) M. p.	Solubility in water. G. in g. water at ° C.	
Glycine	232° dec.	187°	156°	105°	150°	1 : 4·8°.	Acetyl deriv., m. p. 206°; hydantoic acid, m. p. 171°. $FeCl_3$ → red coloration.
Sarcosine	210 dec.	—	—	—	—		
Phenylglycine	126	63	—	—	—		Acetyl deriv., m. p. 194°; nitrosamine, m. p. 105° dec.
Phenylglycine-*o*-carboxylic acid	215 dec.	—	—	—	—		Acetyl deriv., m. p. 214° dec.
Alanine	295	150	151	168	198		Acetyl deriv., m. p. 137°; α-ureidopropionic acid, m. p. 157° dec.
dl-Amino-*n*-butyric acid . .	300 dec.	—	—	—	195	1 : 3·5.	
α-Amino-*iso*butyric acid . .	280 dec.	—	—	—	—	Easily sol.	Acetyl deriv., m. p. 133° dec.
d-Valine	Sublimes and dec.	—	—	—	—	Fairly easily sol.	[α]D +28° in 20% HCl. Chloracetyl deriv., m. p. 113°.
d-Leucine	293	140	146	165	163	1 : 46 at 18°.	[α]D +15° in 20% HCl. Chloracetyl deriv., m. p. 130°.
d-*iso*Leucine	280—290 Sublimes and dec.	116	—	120	178	1 : 25·8 at 15°.	Chloracetyl deriv., m. p. 74°; formyl deriv., m. p. 156°.
dl-Serine	225 dec.	mono- 171 * di- 124	220	—	—	1 : 32 at 10°.	*p*-Nitrobenzoyl deriv., m. p. 190° dec.
l-Phenylalanine	*ca.* 283	—	141	182	—	Difficultly sol.	Formyl deriv., m. p. *ca.* 167°.
l-Tyrosine	290—315	165	254	—	205	1 : 2491.	[α]D —8·6° in 20% HCl. Formyl deriv., m. p. 174°; chloracetyl deriv., m. p. 156°.
Histidine	—	—	—	—	—		Alkaline reaction.
Tryptophane	289	—	—	166	160	Not very sol. cold water.	Picrate, m. p. 195°; picrolonate, m. p. 203°. Cu salt very sparingly sol. Br water → violet coloration. Gives pyrrol reaction.
l-Aspartic acid	270	184	—	—	115	1 : 376 at 0°.	[α]D +6° in water (c, 0·4).
Glutamic acid	206 dec.	132	—	—	236	1 : 100 at 16°.	Acid reaction in water. Hydrochloride, [α]D +30° (c, 4·7). Chloracetyl deriv., m. p. 143°.
Ornithine	—	—	189	—	—		Alkaline reaction. [α]D+16·8° in HCl. Picrate, m.p. 198°.
Arginine	270 dec.	—	—	—	—	Easily sol.	Alkaline reaction. Picrate, m. p. 206°; picrolonate, m. p. 231°. NaOH → urea and ornithine.
Cysteine	—	—	—	—	—		Aq. sol. oxidised by air to cystine. FeCl → indigo-blue coloration.
Cystine	260	—	—	—	—	1 : 8840 at 19°.	Sol. in alkalis pptd. by organic acids, not by mineral acids.
Anthranilic acid	144	181	—	181	—		Acetyl deriv., m. p. 185°; benzenesulphonyl deriv., m. p. 214°; *p*-nitrobenzyl ester, m. p. 205° dec.; phenylacyl ester, m. p. 181°.
m-Aminobenzoic acid . .	174	—	—	264	—		Acetyl deriv., m. p. 250°; benzal deriv., m. p. 119°; *p*-nitrobenzyl ester, m. p. 201°; phenylacyl ester, m. p. 201°.
p-Aminobenzoic acid . .	186	278	—	—	—		Acetyl deriv., m. p. 252°; benzal deriv., m. p. 193°; *p*-nitrobenzyl ester, m. p. 248°; phenylacyl ester, m. p. 211°.
Metanilic acid	280—300 dec.	—	—	—	—	1·27 : 100.	Ba salt, sol. Pb salt, sparingly sol. in water. Acetyl deriv., m. p. 184°, fairly easily sol. in water.
Sulphanilic acid . . .	—	—	—	—	—	1 : 156 at 10°.	Excess Br water → tribromaniline.
Naphthionic acid . . .	—	—	—	—	—	1 : 3448 at 10°.	Dilute aq. sol. Na salt. Violet-blue fluorescence.

CHAPTER VIII

NITRO- AND NITROSO-COMPOUNDS

- (1) Nitro-substituted Hydrocarbons and their Derivatives.
    - (a) Reduction.
        - 1. Formation of β-Hydroxylamines.
        - 2. Formation of Primary Amines.
        - 3. Formation of Azoxy-, Azo-, and Hydrazo-Compounds.
    - (b) Action of Alkali.
    - (c) Special Reactions of Primary and Secondary Nitro-Compounds.
- (2) Nitramines.
- (3) Nitroso-Compounds.
    - (a) *C*-Nitroso-Compounds.
    - (b) *N*-Nitroso-Compounds.
        - 1. Nitrosamines.
        - 2. Nitroso Amides.

(1) *Nitro-substituted Hydrocarbons and their Derivatives.*

In this group of compounds, the nitrogen of the nitro-group $-NO_2$ is attached directly to the carbon. The general formula $>C{\cdot}NO_2$ represents such compounds, of which three types are possible: primary, of the general formula $R{\cdot}CH_2{\cdot}NO_2$; secondary, $RR'CH{\cdot}NO_2$; tertiary, $RR'R''C{\cdot}NO_2$. Although these may be distinguished by special reactions, they all have one reaction in common: the reduction to primary amines.

(a) *Reduction.*

By a suitable choice of experimental conditions, it is possible to obtain either amines or β-hydroxylamines as the primary product of the reduction of nitro-compounds. Other classes of compounds can also be obtained, but they result from secondary reactions during the course of the reduction.

$$R{\cdot}NO_2 \xrightarrow{4H} R{\cdot}NH{\cdot}OH \xrightarrow{2H} R{\cdot}NH_2.$$

1. *Formation of β-Hydroxylamines.*—β-Hydroxylamines are formed to a smaller or greater extent—obviously depending on the experimental conditions—by the reduction of nitroparaffins with stannous chloride and hydrochloric acid (compare E. Hoffmann and V. Meyer, *Ber.*, 1891, **24**, 3531; Züblin, *ibid.*, 1877, **10**, 2083). They are also formed by the electro-reduction at room temperature of alcoholic solutions of nitroparaffins containing sulphuric acid (Pierron, *Bull. Soc. chim.*, 1899, [iii], **21**, 780). Bamberger's process—the use of zinc dust and aqueous ammonium chloride—is a convenient method which is very largely used for the preparation of β-arylhydroxylamines.

Preparation of N-*Methylhydroxylamine.*—Zinc dust (275 g.) is added gradually to a mechanically stirred mixture of nitromethane (100 g.), ammonium chloride (60 g.), and 800 c.c. of water cooled by an external bath of ice-water. The temperature of the reaction mixture should be kept between 0° and 15°, and the addition of the zinc dust should take about 2—3 hours. When the reaction is complete, the paste of zinc and zinc oxide is collected by filtration, the filtrate neutralised with hydrochloric acid and then evaporated on a water-bath till it solidifies on cooling. The hydrochloride of methyl hydroxylamine is isolated therefrom by extraction with absolute alcohol and then adding ether to the clear solution (Beckmann, *Annalen*, 1909, **365**, 204).

Preparation of β-Phenylhydroxylamine.—A suspension of nitrobenzene (60 g.) in 1500 c.c. of water containing 30 g. of ammonium chloride is stirred mechanically and zinc dust (80 g.) added gradually over a period of ¾ hour, the temperature of the mixture being maintained at about 15° throughout the reduction. After about 1 hour, the precipitate is collected and phenylhydroxylamine precipitated from the filtrate by the addition of 400 g. of salt. The crude phenylhydroxylamine is collected, dried on a porous tile, and purified by crystallisation from benzene, m. p. 81°—yield 50 g. (Bamberger, *Ber.*, 1894, **27**, 1548).

This method can be applied to other mononitro-derivatives of homologues of benzene, and the ammonium chloride may be replaced by calcium chloride or magnesium chloride. Other methods of reducing nitro-compounds to hydroxylamines include the action of aluminium amalgam on a moist ethereal solution of the nitro-compound (H. Wislicenus, *Ber.*, 1896, **29**, 494) or the use of zinc amalgam (Bamberger and M. Knecht, *ibid.*, p. 864), or ammonium hydrogen sulphide (Willstätter and Kubli, *ibid.*, 1908, **41**, 1936). An elegant modification of Willstätter and Kubli's method has been worked out by Lapworth and Pearson (*J.*, 1921, **119**, 765) and by R. D. Haworth and Lapworth (*ibid.*, p. 768). This method is illustrated by the following examples.

Preparation of β-Phenylhydroxylamine.—The reagent for the reduction is prepared by adding 10·5 c.c. of concentrated hydrochloric acid to a solution of 27·6 g. of $Na_2S,9H_2O$ in 21·8 c.c. of water, cautiously by the aid of a long funnel, the lower end of which reaches to the bottom of the solution. The solution is contained in a long cylinder and is stirred continuously during the addition of the acid.

For the purpose of reduction, the reagent thus prepared is transferred to a stoppered bottle containing 5 g. of nitrobenzene and a solution of 5 g. of calcium chloride dissolved in the minimum quantity of water. The mixture is shaken vigorously to cause an emulsion, keeping the temperature of mixture below 30°. It is shaken occasionally to maintain the emulsion. The liquid becomes thicker and the colour gradually darkens to deep orange. It is examined at frequent intervals with a lens to ascertain when the oily drops have disappeared. When this phase is reached—usually after 1½ hours—6 g. of ammonium chloride are added and the mixture is shaken to completely dissolve the inorganic matter. The precipitate of crystalline β-phenylhydroxylamine is collected—yield 72—74% of theoretical (Pearson and Lapworth, *loc. cit.*).

When solid nitro-compounds are used benzene is used as a solvent.

*Preparation of β-*p*-Chlorophenylhydroxylamine.*—A solution of 11 g. of *p*-chloronitrobenzene in 15 c.c. of benzene is mixed with 115 g. of sodium hydrogen sulphide solution and the whole emulsified by shaking with a solution of 10 g. of calcium chloride in water. The temperature is kept below 30° by external cooling. After about 1½ hours, 10 g. of solid ammonium chloride are added, the mixture is shaken and filtered. Almost pure *p*-chlorophenylhydroxylamine is thus obtained. It is purified by crystallisation from benzene, m. p. 86—87°—yield 6·5—7 g. (Haworth and Lapworth, *loc. cit.*).

These methods of obtaining hydroxylamines are not altogether satisfactory when applied to dinitro-compounds, to nitranilines, or to nitrophenols (Cohen and McCandlish, *J.*, 1905, **87**, 1257).

2. *Formation of Primary Amines.*—Reduction of nitro-compounds can be achieved by the use of acid reducing agents such as tin and hydrochloric acid, stannous chloride and acid, zinc and hydrochloric acid, iron with either hydrochloric acid or acetic acid. Other reducing agents sometimes used are alkali sulphides, titanous chloride, or zinc dust in boiling aqueous alcohol containing ammonium chloride.

The reducing agent most commonly employed for laboratory purposes is tin and hydrochloric acid. In order to provide the requisite amount of hydrogen for the reduction after taking into account the reducing action of the stannous chloride which is formed, it is necessary to use at least 1·5 atomic proportions of tin for every nitro-group. In practice, at least 1½ times the theoretical quantity of tin is used.

The general method of procedure is to add concentrated or moderately concentrated hydrochloric acid to a mixture of the nitro-compound and granulated tin. It is advisable to moderate the violence of the reaction so as to prevent the partial elimination of the nitro-group as ammonia. When the reaction is complete, a double compound of the amine hydrochloride and tin chloride may separate. The method adopted for the isolation of the product depends largely on the properties of the amine formed. If it is volatile in steam it is usually isolated by adding an excess of concentrated alkali and distilling in steam. An alternative method, applicable to any amine soluble in ether, is to add sufficient alkali to dissolve the tin hydroxides and then to extract with ether. This process has the disadvantage that troublesome emulsions may be formed. A more convenient method is to precipitate the tin, after diluting and partially neutralising, by saturating the solution with hydrogen sulphide. When the solution is free from tin, it is filtered and evaporated, and the free base isolated by adding an excess of alkali.

With very sparingly soluble nitro-compounds it is sometimes advantageous to add some acetic acid or alcohol to facilitate the reduction.

In place of tin and hydrochloric acid, a solution of stannous chloride in hydrochloric acid may be used, the nitro-compound being dissolved in a suitable solvent. This form of reduction has the advantage that with dinitro- and trinitro-compounds a selective reduction of one nitro-group can be effected by adding the calculated amount of the reducing agent. Thus 2 : 4-dinitrotoluene yields 4-nitro-*o*-toluidine (Anschütz, *Ber.*, 1886, **19**, 2116), while 2 : 3-dinitrotoluene furnishes 2-nitro-*m*-toluidine. On the other hand, 3 : 4-dinitro- and 2 : 5-dinitro-toluenes yield mixtures of nitroamines under the same conditions (Kenner and Burton, *J.*, 1921, **119**, 1051).

The reduction of aromatic nitro-compounds by tin and hydrochloric acid has the disadvantage that the product may contain smaller or greater amounts of chloro-substituted amine. This applies also when zinc and hydrochloric acid are used. Thus Kock (*Ber.*, 1887, **20**, 1567) found that considerable amounts of *p*-chloroaniline were produced by the reduction of nitrobenzene with zinc and hydrochloric acid. When *p*-nitrophenetole is reduced with tin and concentrated hydrochloric acid a 90% yield of 3-chloro-*p*-phenetidine is obtained if the reaction is allowed to proceed without cooling. If, however, diluted hydrochloric acid is used, *p*-phenetidine results without any chloro-substituted amine (Hurst and Thorpe, *J.*, 1915, **107**, 934; compare Fittig, *Ber.*, 1875, **8**, 15; Beilstein and Kuhlberg, *Annalen*, 1870, **156**, 81; Jannasch, *ibid.*, 1875, **176**, 55). Apparently the production of chlorinated amines can be effected without using hydrochloric acid, for de Kiewiet and H. Stephen (*J.*, 1931, 82), using a solution of stannous chloride in acetic anhydride as the reducing agent, found that nitrobenzene yields *p*-chloroacetanilide as the principal product. *o*- and *m*-Nitrotoluenes and *o*-nitroanisole and *o*-nitrophenetole behave similarly. *p*-Nitrotoluene, *p*-nitroanisole, and *p*-nitrophenetole are smoothly reduced without the formation of halogen-substituted products.

Preparation of p-*Chloroacetanilide from Nitrobenzene.*—Crystalline stannous chloride (3·5 g.—3 mols.) is treated with acetic anhydride (4·6 g.—9 mols.) in a Claisen flask. When dehydration is complete (see Stephen, *J.*, 1930, 2786) nitrobenzene (0·6 g., 1 mol.) is added and the mixture heated till a clear yellow solution is obtained. The acetic acid is removed under reduced pressure and the residue treated with water till a clear solution is obtained. On cooling, *p*-chloroacetanilide is obtained in almost theoretical yield, m. p. 175° (de Kiewiet and Stephen, *loc. cit.*).

It sometimes happens that the use of tin and hydrochloric acid may result in the removal of halogen when halogen-substituted nitro-aromatic compounds are reduced. Thus 4-bromo-1 : 3-dinitrobenzene gives *m*-phenylenediamine. The use of iron and a small amount of hydrochloric acid, however, gives the normal reduction product—1-bromo-2 : 4-phenylenediamine (Zincke and Sintenis, *Ber.*, 1872, **5**, 792; Morgan, *J.*, 1900, **77**, 1202; compare Blanksma, *Rec. trav. chim.*, 1905, **24**, 320).

When the nitro-compound is sensitive to the action of warm mineral acids, or if it is desired to avoid the formation of undesirable by-products iron and acetic acid or some similar acid may be used very conveniently for the reduction. This method appears to have been used first by Béchamp (*Annalen*, 1854, **92**, 401) for the reduction of nitrobenzene and nitronaphthalene. In addition, iron may be used for reduction in conjunction with only a small quantity of dilute hydrochloric acid.

Preparation of Formyl-p-*phenylenediamine.*—*p*-Nitroformanilide (20 g.) is suspended in 70 c.c. of hot water containing 1 g. of formic acid. Iron borings (20 g.) are slowly added. The reduction is complete after about 40 minutes. 1 G. of calcium carbonate is then added and the precipitate of iron hydroxides rapidly filtered from the boiling solution. The filtrate deposits 6—7 g. of formyl-*p*-phenylenediamine on cooling. The remainder is obtained by evaporating the solution. The base is purified by extraction with benzene in a Soxhlet apparatus, m. p. 125—126° (Morgan and Upton, *J.*, 1917, **111**, 190).

*Preparation of Benzoyl-*o*-phenylenediamine.*—Iron borings (60 g.) and 5% aqueous acetic acid (65 c.c.) are warmed together in a dish till the evolution of hydrogen has slackened somewhat, when 24 g. of benzoyl *o*-nitraniline are added in small quantities, the mass being well stirred. When all the nitro-compound has been added the reaction mixture is heated on a water-bath for 1 hour, and then neutralised with sodium carbonate. After cooling, it is filtered and the solid residue extracted with alcohol. Evaporation of the alcoholic extract furnishes benzoyl-*o*-phenylenediamine (F. H. Witt, *Ber.*, 1912, **45**, 2382).

Preparation of 1-*Bromo*-2 : 4-*diaminobenzene*.—An excess of iron filings is slowly added to 40 g. of 1-bromo-2 : 4-dinitrobenzene suspended in 400 c.c. of hot water acidified with 5 c.c. of concentrated hydrochloric acid. The mixture is shaken continually during the operation. The dinitro-compound gradually disappears, the solution darkens, and considerable heat is developed, 400 c.c. of cold water being added during the reduction to moderate the reaction. When the nitro-compound has gone, the mixture is heated on a sand-bath and 10 g. of sodium carbonate are added. The solution is then rapidly filtered and the precipitate of oxides of iron and unchanged iron is washed with 100 c.c. of boiling water. The total filtrate is cooled in ice and salt. After several hours, the bromodiamine separates—yield 14—15 g. A further amount is obtained by extracting the aqueous solution with chloroform. The amine separates from benzene as irregular clusters of acicular prisms, m. p. 111—112° (Morgan, *J.*, 1900, **77**, 1204).

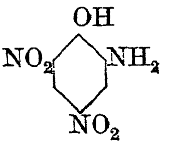
The use of iron borings and dilute hydrochloric acid finds application in the industrial reduction of nitro-compounds, but in this case only a fraction of the theoretical amount of hydrochloric acid is needed. Although several explanations have been advanced to account for this, the most satisfactory appears to be that of Raikow (*Z. angew. Chem.*, 1916, **29**, i, 196, 239), who represents the course of the reduction by the following equations :

$$3Fe + 6HCl + PhNO_2 \longrightarrow 3FeCl_2 + PhNH_2 + 2H_2O$$
$$3FeCl_2 + 2H_2O \longrightarrow [3Fe(OH)_2 + 6HCl]$$
$$[3Fe(OH)_2 + 6HCl] + 3Fe + PhNO_2 \longrightarrow 3Fe(OH)_2 + 3FeCl_2 + PhNH_2 + H_2O$$

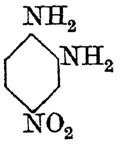
The reduction is therefore dependent on the hydrolysis of ferrous chloride. In support of this view, it has been found possible to reduce nitro-compounds with iron and aqueous solutions of such salts as magnesium chloride or ferric chloride. Even potassium or sodium chloride can serve as the source of chloridion (Lyons and L. T. Smith, *Ber.*, 1927, **60**, 173; Bretnütz and Pensa, *Z.*, 1927, ii, 243).

The sulphides and polysulphides of the alkali metals and of ammonium can reduce aromatic nitro-compounds to amines, a reaction which appears to have been first employed by Zinin (*J. pr. Chem.*, 1842, [i], **27**, 140; *Annalen*, 1842, **44**, 283).

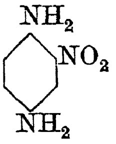
Reduction with ammonium sulphides is generally effected by solution of the nitro-compound in aqueous alcoholic ammonia and subsequent saturation with hydrogen sulphide. Under these conditions mononitro-compounds are reduced but slowly at room temperature (compare Cohen and McCandlish, *J.*, 1905, **87**, 1257). Dinitro-compounds react more readily, and this process is generally applied to them, more particularly for the reduction of one of the nitro-groups. Thus *m*-dinitrobenzene is smoothly reduced to *m*-nitraniline; 2 : 4-dinitrotoluene yields 2-nitro-*p*-toluidine. In general it appears that a nitro-group having some substituent *ortho* to it is less easily reduced than others not so situated, but to this generalisation there are many exceptions. Thus picric acid gives picramic acid (I) (Girard, *Annalen*, 1853, **88**, 261), while 2 : 4-dinitraniline gives a mixture of 4-nitro-*o*-phenylenediamine (II) and 2-nitro-*p*-phenylenediamine (III) (Kehrmann, *Ber.*, 1895, **28**, 1707). The use of ammonium sulphide has the disadvantage that if the nitro-group is labile, it may suffer replacement as in 2 : 3-dinitrotoluene (IV), which gives dinitroditolylsulphide (Kenner and Parkin, *J.*, 1920, **117**, 857).



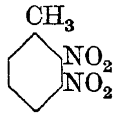
(I.)



(II.)



(III.)



(IV.)

Preparation of m-*Nitraniline from* m-*Dinitrobenzene.*—A solution of 20 g. of *m*-dinitrobenzene in 100 g. of boiling alcohol in a round-bottomed flask is cooled and 17·5 c.c. of 24% aqueous ammonia are added. The flask and its contents are weighed, and then hydrogen sulphide passed in till the solution is saturated. It is then heated under reflux for ½ hour in a boiling water-bath. Repeat the operation of saturating with hydrogen sulphide and heating under reflux till the increase in weight is 12 g. The solution is then diluted with water and the precipitate which is thus obtained is collected and extracted repeatedly with dilute warm hydrochloric acid. The combined acid extracts are rendered alkaline by the addition of ammonia. *m*-Nitraniline is liberated, and after collection by filtration, it is purified by crystallisation from water, m. p. 114°.

Preparation of 3 : 5-*Dinitraniline from* 1 : 3 : 5-*Trinitrobenzene.*—A solution of alcoholic ammonium sulphide is prepared by passing hydrogen sulphide into a mixture of 100 g. of absolute alcohol and 54 g. of concentrated ammonia till the concentration of hydrogen sulphide is 7·7% by weight. The solution so prepared is added to a solution of 15 g. of trinitrobenzene in 300 c.c. of vigorously boiling alcohol and the mixture boiled for 1½ hours. After cooling, the sulphur is collected by filtration, the alcohol removed by distillation, and the residue extracted several times with hot water under reflux—yield 7 g., m. p. 154—157° (Flürsheim, *J. pr. Chem.*, 1905, [ii], **71**, 537).

Preparation of 4-*Nitro*-2-*aminomethylaniline.*—2 : 4-Dinitromethylaniline (5 g.) is added to a mixture of pyridine (50 c.c.) and concentrated ammonia (5 c.c.). The suspension is saturated with hydrogen sulphide and then warmed to 100°. The current of the gas is continued for 2 hours, when as much as possible of the pyridine is removed by distillation under reduced pressure at 100°. The residue is shaken with 100 c.c. of water and the red solid obtained is washed with water and repeatedly extracted with small quantities of boiling 2*N*-hydrochloric acid. The extracts are concentrated to 100 c.c., cooled to 0°, and made alkaline with ammonia. The precipitated base is recrystallised from hot water (Brady, Day, and Reynolds, *J.*, 1929, 2264).

Preparation of Nitromesidine from Dinitromesitylene.—A solution of crystalline sodium sulphide (6 g.) and sulphur (0·8 g.) in 15 c.c. of water is added, over a period of 2 hours, to a mechanically stirred suspension of 5 g. of dinitromesitylene in 18 c.c. of boiling water. The reduced product is poured into 20 c.c. of cold water and acidified with dilute hydrochloric acid. The precipitated sulphur is extracted several times with dilute hydrochloric acid. The combined filtrate and extracts yield nitromesidine on adding an excess of dilute ammonia, m. p. 73° (Morgan and Davies, *J.*, 1923, **123**, 231; compare Flürsheim, *J.S.C.I.*, 1912, **31**, 66).

Ferrous sulphate in alkaline solution has been used successfully for the reduction of nitro-compounds—particularly acids—which are sensitive to the action of acid reducing agents. Thus it has been used for the reduction of the nitro-group in nitrobenzoylformic acid (Claisen and Thompson, *Ber.*, 1879, **12**, 1946), *o*-nitrophenylpropiolic acid, nitrobenzaldehyde, and the nitro-cinnamic acids (Baeyer and Bloem, *Ber.*, 1882, **15**, 2147; Gabriel, *ibid.*, p. 2294; Bamberger and Demuth, *ibid*, 1901, **34**, 1330; Stoermer and Heymann, *ibid.*, 1912, **45**, 3102). The following general directions are given by Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1917, **39**, 1435) for this purpose.

A solution of the substance in dilute ammonia, or in the case of amides a suspension in water or dilute ammonia, is poured into a boiling solution of 7 mol. equivalents of crystalline ferrous sulphate in 2—2·5 parts of water. The solution is then treated with small portions of concentrated ammonia, each addition being followed by a vigorous agitation of the mixture. When the solution is distinctly alkaline it is boiled for 5 minutes and filtered hot under suction, more ammonia being added if it is no longer alkaline. The subsequent treatment depends on the substance which is being reduced. Some amino-compounds separate on cooling the filtrate. If the product is an amino-acid it is usually necessary to concentrate to a small bulk under reduced pressure and then to acidify with acetic acid.

A method of reduction which has been employed successfully for the reduction of nitro-acyl amines and nitro-ketones is to heat the nitro-compound in aqueous alcoholic solution containing some ammonium chloride with zinc dust.

Reduction of the p-*Toluenesulphonyl Derivative of* 1-*Nitro-β-methylnaphthylamine.*—The nitro-compound (20 g.) is suspended in a mixture of 200 c.c. of alcohol and 20 c.c. of water containing 4 g. of ammonium chloride. Zinc dust (27 g.) is added and the solution boiled for 2 hours. After filtration to remove suspended matter, the base is precipitated by the addition of water to the filtrate. It separates from alcohol in transparent prisms, m. p. 140—141° (Morgan and Micklethwait, *J.*, 1912, **101**, 151; compare Morgan and Hickinbottom, *ibid.*, 1921, **119**, 1883).

Titanous chloride has been used for the reduction of nitro-groups in the aromatic nucleus and also for the selective reduction of dinitro-compounds (F. Sachs and Sichel, *Ber.*, 1904, **37**, 1862). Its principal use is for the estimation of nitro-groups (E. Knecht, *Ber.*, 1903, **36**, 166; Knecht and E. Hibbert, *ibid.*, p. 1549).

In addition to the methods of reduction discussed above, reduction of nitro-compounds to amines has also been effected by catalytic methods. The reduction of nitrobenzene and its homologues in the vapour phase by hydrogen has been the subject of numerous patents. Metallic copper, ferrous oxide, iron, gold, silver, nickel, and platinum are claimed to be suitable catalysts for this purpose. For laboratory preparations, hydrogenation in the liquid phase is more suitable. The reduction may be effected in ethereal or alcoholic solution using platinum-black and molecular hydrogen (Cusmano, *Atti R. Accad. Lincei*, 1917, [v], **26**, ii, 87; Brand and Steiner, *Ber.*, 1922, **55**, 875; R. Adams, F. L. Cohen, and Rees, *J. Amer. Chem. Soc.*, 1927, **49**, 1093). The intermediate phase in this reduction appears to be a β-arylhydroxylamine. The method has been applied to the selective reduction of dinitro-compounds (Vesely and Rein, A., 1927, 757).

Some aliphatic primary and secondary nitro-compounds yield appreciable amounts of an aldehyde or ketone in addition to the corresponding amine by reduction with zinc or tin and hydrochloric acid. Thus nitro*cyclo*hexane is converted by these reducing agents into a mixture of amino*cyclo*hexane, ammonia, and *cyclo*hexanone (Markovnikoff, *Annalen*, 1898, **302**, 18, 22; compare Wallach, 1904, **336**, 3; **332**, 323).

The formation of a carbonyl compound is effected more completely by adding a solution of the alkali salt of the nitro-compound to a cold solution of stannous chloride in fuming hydrochloric acid and subsequently steam distillating. The reaction is due to the reduction of the *iso*nitro-compound to an oxime, which then undergoes hydrolysis by the action of the excess of acid during the distillation (Konovaloff, *J. Russ. Phys. Chem. Soc.*, 1899, **30**, 960).

$$RR'C{:}NO{\cdot}OH \xrightarrow{2H} RR'C{:}NOH \xrightarrow{H_2O} RR'C{:}O + NH_2OH.$$

If the mixture is carefully neutralised with sodium carbonate after the reduction is complete, the oxime can be isolated (v. Braun and Sobecki, *Ber.*, 1911, **44**, 2533; v. Braun and Kruber, *ibid.*, 1912, **45**, 394). Other methods which have been used for the reduction of *iso*nitro-compounds to oximes include the action of sodium amalgam at low temperatures (Bamberger and Weiler, *J. pr. Chem.*, 1898, [ii], **58**, 333), zinc dust in alkaline solution, or aluminium amalgam, or sodium and alcohol (Hantzsch and O. W. Schultze, *Ber.*, 1896, **29**, 2252).

3. *Formation of Azoxy-, Azo-, and Hydrazo-compounds.*—In the processes for the reduction of aromatic nitro-compounds so far discussed, the action has been to produce an amino-compound or a hydroxylamine. By choosing suitable conditions, products can be obtained containing two aryl groups, such as azoxy-compounds $R{\cdot}NO{:}N{\cdot}R$, azo-compounds $R{\cdot}N{:}N{\cdot}R$, and hydrazo-compounds $R{\cdot}NH{\cdot}NH{\cdot}R$. In general, such compounds are formed by reduction in alkaline media, or at least in the absence of free acids.*

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* It is, however, possible to prepare some azoxy-compounds by reduction with stannous chloride and acid under suitable conditions (Flürscheim, *J. pr. Chem.*, 1905, [ii], **71**, 514; compare also E. Heller, *ibid.*, 1908, **41**, 2690).

The production of compounds of this type appears to be due to the intermediate formation of nitro-compounds and β-hydroxylamines which undergo condensation to azoxy-compounds.

$$R{\cdot}NO + R{\cdot}NHOH \longrightarrow R{\cdot}N{:}NO{\cdot}R + H_2O.$$

Reduction of the azoxy-compound to azo- and hydrazo-compounds then takes place fairly easily under suitable conditions. An excellent summary of the general conditions governing this type of end product in the reduction of nitro-compounds is given by Sidgwick (*Organic Chemistry of Nitrogen*, pp. 155–162).

Nitrobenzene is reduced by the action of boiling alcoholic potash yielding azoxybenzene (Zinin, *J. pr. Chem.*, 1845, [i], **36**, 98; H. Schmidt and G. Schultz, *Annalen*, 1881, **207**, 328).

$$4Ph{\cdot}NO_2 + 3NaOCH_3 \qquad 2Ph{\cdot}NO{:}N{\cdot}Ph + 3NaOOC{\cdot}H + 3H_2O.$$

Preparation of Azoxybenzene.—A mixture of 200 g. of methyl alcohol, 40 g. of sodium hydroxide, and 30 g. of nitrobenzene are boiled under reflux for several hours till a portion of the solution no longer smells of nitrobenzene when it is diluted. The solvent is then distilled off and the residue poured into water. The crude azoxybenzene is deposited as a dark oil, which soon solidifies. It is washed several times with water and then drained on a porous tile. It crystallises from methyl alcohol as pale yellow needles, m. p. 36° yield about 80% of theory (Klinger, *Ber.*, 1882, **15**, 865; Lachmann, *J. Amer. Chem. Soc.*, 1902, **24**, 1180).

The yield of azoxybenzene is stated to be improved if the nitrobenzene is heated with an excess of dry sodium methoxide suspended in xylene (Brühl, *Ber.*, 1904, **37**, 2076).

The preparation of other azoxy-compounds by reduction of the nitro-compound with sodium alcoholate is restricted in its application. Thus *p*-nitrotoluene yields stilbene derivatives (O. Fischer and Hepp, *Ber.*, 1893, **26**, 2231); *p*-nitrophenetole suffers partial replacement of the ethoxy-group by the action of sodium methoxide (Gattermann and Ritschke, *Ber.*, 1890, **23**, 1738). *o*- and *p*-Nitrochlorobenzenes yield the corresponding azoxy-compounds by this method if suitable conditions are chosen, otherwise there is a more or less complete replacement of the halogen (Willgerodt, *Ber.*, 1882, **15**, 1002; Brand, *J. pr. Chem.*, 1903, [ii], **67**, 145; compare also Klinger and Pitschke, *Ber.*, 1885, **18**, 255; Lobry de Bruyn, *Rec. trav. chim.*, 1885, **2**, 235).

Azoxybenzene can be prepared from nitrobenzene by the use of magnesium amalgam and alcohol. This method can be applied to the preparation of the azoxy-toluenes from the corresponding nitro-compounds (Evans and Fry, *J. Amer. Chem. Soc.*, 1904, **26**, 1161). Calcium and alcohol has also been used as a reducing agent for this purpose (Beckmann, *Ber.*, 1905, **38**, 904).

Some aminoazoxy-compounds have been prepared by the reduction of nitro-amines with sodium amalgam and alcohol (Buckney, *Ber.*, 1878, **11**, 1452; Limpricht, *ibid.*, 1885, **18**, 1405), or with zinc dust and alcoholic ammonia (Mixter, *J. Amer. Chem. Soc.*, 1883, **5**, 1, 282).

Aqueous sodium arsenite has been found to be effective for the reduction of nitrobenzene and nitrobenzenesulphonic acids to azoxy-compounds. *p*-Nitrotoluene, however, is reduced to *p*-toluidine, while *o*-nitrotoluene is not affected (Lösner, *J. pr. Chem.*, 1894, [ii], **50**, 564; Snowdon, *J. phys. Chem.*, 1911, **15**, 842).

Preparation of Azoxybenzene.—A mixture of 25 g. of nitrobenzene, 30 g. of arsenious oxide, 40 g. of sodium hydroxide, and 400 c.c. of water is boiled under reflux and stirred mechanically for 8 hours. The oil is then separated from the aqueous layer, washed with water and dilute hydrochloric acid, and steam distilled. Nitrobenzene passes over first, followed by azoxybenzene—yield 60—70% of theory (Lösner, *loc. cit.*).

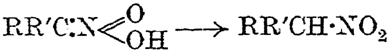
A method of fairly general application for the preparation of azo-compounds from nitro-compounds is the use of alkaline stannite solution (Witt, *Ber.*, 1885, **18**, 2912). The method consists in dissolving the necessary amount of stannous chloride in an excess of sodium hydroxide and then adding the clear solution to the nitro-compound in alcohol; or the nitro-compound can be suspended in the alkaline solution, while it is stirred and heated on a water-bath under reflux. When the reduction is complete, the unchanged nitro-compound is distilled off in steam, and the azo-compound collected by filtration.

Azo-compounds are also formed by the reduction of nitro-compounds with zinc dust and alkali, usually in presence of alcohol. Under these conditions, hydrazo-compounds are also formed, but as they are readily oxidised in air, it is possible to use the process either for the preparation of hydrazo- or of azo-compounds (Alexejeff, *Jahresb.*, 1868, 740).

Preparation of Hydrazobenzene.—Nitrobenzene (50 g.), alcohol (50 g.), and a solution of 54 g. of sodium hydroxide in 200 c.c. of water are mixed in a round-bottomed flask fitted with a reflux condenser and a mechanically driven stirrer fitted with a mercury seal. While the mixture is stirred vigorously, zinc dust is added through the condenser or through a special tube fitted with a cork. The zinc dust should be added in amounts of about 3—4 g. at a time, and the rate of addition should be regulated so that the reaction mixture does not unduly froth. The reaction is continued till the red colour of the solution has become a pale yellow. The reaction mixture is then diluted with water (1 l.), the precipitate of zinc residues and hydrazobenzene collected by filtration and washed with water till free from alkali. The hydrazobenzene is then extracted from the precipitate by boiling alcohol (750 c.c.) under reflux. After filtering, the filtrate is cooled in a freezing mixture. Hydrazobenzene separates as colourless plates, m. p. 125°. A further amount may be obtained by using the mother-liquor for the further extraction of the zinc residues.

(b) *Action of Alkali.*

Although the nitro-paraffins are neutral compounds, those of the general formula $\mathrm{RR'CH{\cdot}NO_2}$ can yield, by reaction with aqueous alkali, sodium salts represented by the general formula $\mathrm{RR'C{:}N{<}^{O}_{ONa}}$. This serves to distinguish primary and secondary nitro-compounds from tertiary which are incapable of forming such salts. On acidification, the salts derived from primary and secondary nitro-compounds liberate the *aci-* or *iso*nitro-form $RR'C{:}N{<}^{O}_{OH}$, which on keeping reverts more or less readily to the original neutral nitro-compound



$$RR'C{:}N{<}^{O}_{OH} \longrightarrow RR'CH{\cdot}NO_2.$$

In the aliphatic series the change of *aci*-form to nitro-compound proceeds so rapidly that the free *aci*-form cannot be isolated, although it has been followed, for nitromethane, by measurements of the conductivity (Hantzsch and Veit, *Ber.*, 1900, **32**, 607). The conversion of the *aci*-form of aryl-substituted nitroparaffins to the neutral nitro-compound is sufficiently slow to allow of the isolation of many of them in both forms. Thus, by adding an excess of dilute mineral acid to an ice-cold solution of the sodium salt of the *aci*-form of phenylnitromethane, the free *iso*nitro-compound $Ph{\cdot}CH{:}NO(OH)$ is obtained as a white crystalline solid, m. p. 84°. This substance differs from the neutral form of phenylnitromethane in giving an intense red colour with ferric chloride and a brownish-red copper salt with cupric acetate in aqueous alcoholic solution. The solid *iso*nitro-compound changes to the normal form on keeping, and the change can be followed by periodical measurements of the conductivity. Thus the sodium salt derived from phenylnitromethane and the equivalent amount of hydrochloric acid at 0° gave the following values for the conductivity, $v = 64$.

Time (in mins.)	3	5	20	60	95	145	180
μ.................	69·6	68·1	67·0	63·7	62·7	62·1	62·0

The final value is that of sodium chloride (Hantzsch and Schultze, *Ber.*, 1896, **29**, 700). Both forms of xylylnitromethane (3 : 5-dimethylphenylnitromethane) are known. The *iso*nitro-compound separates as white needles, m. p. about 63°, by the addition of dilute sulphuric acid to an ice-cold solution of the nitro-compound in dilute alkali. It changes to the normal form, m. p. 47°, on warming (Konovaloff, *Ber.*, 1896, **29**, 2194).

The following papers on *iso*nitro-compounds should also be consulted: Nef, *Annalen*, 1892, **270**, 331; Hantzsch, *Ber.*, 1899, **32**, 575; Hantzsch and Rinkenberger, *ibid.*, p. 628; Holleman, *ibid.*, 1900, **33**, 2913.

A reaction of primary and secondary nitro-compounds, due to Konovaloff, which obviously depends on the formation of salts of the *iso*nitro-form, is carried out as follows.

The nitro-compound is treated with a little concentrated potassium hydroxide solution or with an alcoholic solution of sodium ethoxide. The resulting salt is extracted with a small quantity of water and the aqueous extract covered with ether. Ferric chloride solution is now added drop by drop, the solution being shaken during the addition. At first there is formed a precipitate of ferric hydroxide, and then the ether assumes a red or reddish-brown colour (*Ber.*, 1895, **28**, 1851).

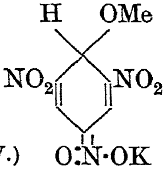
The aromatic mononitro-derivatives of benzene and its homologues are indifferent to cold aqueous alkali, and thus resemble the tertiary nitro-paraffins. The presence of two or more nitro-groups in the nucleus appears to make them more reactive to alkalis. Thus 1 : 3 : 5-trinitrobenzene gives a red colour with alkali, and it finds a limited application as an indicator in acidimetry and alkalimetry. A number of colour reactions of di- and tri-nitro-substituted aromatic hydrocarbons and their derivatives have been described, which are based on this property of giving colorations with alkalis.

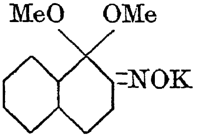
Janovsky's Reaction.—A solution of the nitro-compound in acetone is shaken with 10% aqueous potassium hydroxide solution. *m*-Dinitrobenzene gives a reddish-violet coloration; 2 : 4-dinitrotoluene, a royal blue; 1 : 3 : 5-trinitrobenzene, a blood-red; 2 : 4-dinitrochlorobenzene, red changing to lilac (Janovsky and Erb, *Ber.*, 1886, **19**, 2158; Janovsky, *ibid.*, 1891, **24**, 971).

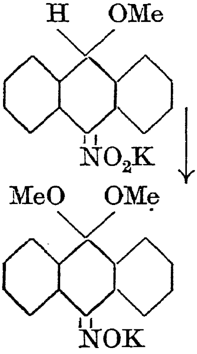
A similar type of colour reaction is described by v. Bittó (*Annalen*, 1892, **269**, 377), who replaces the acetone by other ketones and by aldehydes (compare Reitzenstein and Stamm, *J. pr. Chem.*, 1910, [ii], **81**, 167). Alcoholic potash also gives intense colorations with many dinitro- and trinitro-compounds. These are due to the formation of additive compounds between the nitro-compound and the alcoholic potash. Thus 1 : 3 : 5-trinitrobenzene in methyl alcohol furnishes a red crystalline compound of the formula

$$(C_6H_3(NO_2)_3,CH_3\cdot OK)_2,H_2O$$

when treated with one molecular proportion of potash (Lobry de Bruyn, *Rec. trav. chim.*, 1895, **14**, 89, 151; Hantzsch and Kissel, *Ber.*, 1899, **32**, 3140). This compound and others of a similar type formed from other trinitro-compounds are formulated by Meisenheimer (*Annalen*, 1902, **323**, 224) as (V). It is of interest to note


(V.)


(VI.)


(VII*a*.)

(VII*b*.)

$Ph\cdot CH(OMe)\cdot CH{:}NO_2K$

(VIII.)

that while mononitrobenzene or α-nitronaphthalene give no such compounds with alcoholic potash, β-nitronaphthalene and 9-nitroanthracene yield the compounds (VI) and (VII), respectively

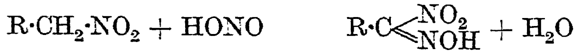
(Meisenheimer, *loc. cit.*, p. 214; Meisenheimer and Witte, *Ber.*, 1903, **36**, 4164).

Some unsaturated aliphatic nitro-compounds are also capable of combining additively with sodium ethoxide or methoxide. Thus ω-nitrostyrene gives the compound (VIII) with sodium methoxide (Meisenheimer and Heim, *Ber.*, 1905, **38**, 466; compare Thiele and Haeckel, *Annalen*, 1902, **325**, 1; Wieland, *Ber.*, 1904, **37**, 1148).

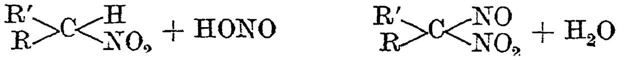
(*c*) *Special Reactions of Primary and Secondary Nitro-compounds.*

The behaviour of nitro-compounds towards alkali has already been discussed, and methods for distinguishing primary and secondary nitro-compounds from tertiary ones based on such reactions have been indicated. The following paragraphs give an account of other reactions which distinguish the three classes of compounds.

Action of Nitrous Acid.—Primary nitro-compounds yield nitrolic acids by the action of nitrous acid under suitable conditions (equation *a*). Similarly, secondary nitro-compounds furnish ψ-nitroles (equation (*b*)). Tertiary nitro-compounds are unaffected under the conditions which yield the nitrolic acids or ψ-nitroles.



$$R{\cdot}CH_2{\cdot}NO_2 + HONO \qquad R{\cdot}C{<}\genfrac{}{}{0pt}{}{NO_2}{NOH} + H_2O \qquad (a)$$



$$\genfrac{}{}{0pt}{}{R'}{R}{>}C{<}\genfrac{}{}{0pt}{}{H}{NO_2} + HONO \qquad \genfrac{}{}{0pt}{}{R'}{R}{>}C{<}\genfrac{}{}{0pt}{}{NO}{NO_2} + H_2O \qquad (b)$$

As the nitrolic acids yield red salts with dilute aqueous alkali, and the nitroles are blue in the liquid state, this reaction serves to distinguish the three classes of compound (V. Meyer, *Annalen*, 1875, **175**, 120; Meyer and Locher, *ibid.*, 1876, **180**, 136; Meyer and Constam, *ibid.*, 1882, **214**, 328; Tscherniac, *ibid.*, 1876, **180**, 166). The test is usually carried out as follows.

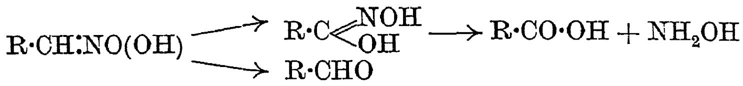
The nitro-compound is dissolved in concentrated alkali containing sodium nitrite. After diluting a little, dilute sulphuric acid is added drop by drop. If a primary nitro-compound is present, the solution assumes a blood-red colour, which disappears on complete acidification. It reappears on making alkaline.

Secondary nitro-compounds yield a blue or a blue-green coloration which can be extracted with chloroform.

This test is stated to hold for primary nitro-paraffins up to nitrohexadecane; for secondary nitro-compounds it is apparently of less general application.

Preparation of Ethyl Nitrolic Acid.—Nitroethane (6 c.c.) is mixed with crushed ice in a small thick-walled glass bottle, and 15 c.c. of an aqueous solution of potassium hydroxide containing 5·6 g. of potash are added. The bottle is closed by a rubber stopper and shaken till the nitroethane dissolves, a rise in temperature being carefully avoided. The solution is transferred to a beaker, an excess of sodium nitrite solution added, and the mixture is cooled to 0° by the addition of ice. Dilute sulphuric acid is added slowly till the solution is colourless or just pale yellow. In order to convert all the nitroethane into the nitrolic acid it is necessary to render the solution alkaline and acidify; this operation is repeated three times. The feebly acid solution is finally extracted three times with one-sixth of its volume of ether, each time. The ethereal solution, on spontaneous evaporation, yields ethylnitrolic acid, colourless crystals, m. p. 81—82° with decomposition. The yield may amount to 10—11 g. of 12 c.c. of nitroethane (Meyer and Constam, *loc. cit.*).

Reaction of Aliphatic Nitro-compounds with Aqueous Acids.—Although the careful acidification of the sodium salt of *iso*nitroethane results in the liberation of nitroethane almost unchanged, smaller or greater amounts of acetaldehyde are obtained when the acidification is rapid and the mixture is not cooled. A transient blue or green coloration is also produced. The alkali salts derived from nitromethane behave similarly (Nef, *Annalen*, 1894, **280**, 267; V. Meyer, *Ber.*, 1895, **28**, 202). The decomposition may also take another course—a hydroxamic acid being formed (Bamberger and Rüst, *Ber.*, 1902, **35**, 52; Bamberger, *J. pr. Chem.*, 1920, [ii], **101**, 328). This has been shown to occur when the alkali salts derived from many nitroparaffins are treated with diluted hydrochloric or sulphuric acids.



$$R\cdot CH{:}NO(OH)\begin{array}{l}\nearrow R\cdot C{<}^{NOH}_{OH} \longrightarrow R\cdot CO\cdot OH + NH_2OH\\ \searrow R\cdot CHO\end{array}$$

The formation of a hydroxamic acid is obviously responsible for the recorded observations that many nitroparaffins yield hydroxylamine and fatty acids when heated with concentrated hydrochloric or sulphuric acids in sealed tubes (Meyer and Locher, *Annalen*, 1873, **180**, 163; compare Preibisch, *J. pr. Chem.*, 1873, [ii], **7**, 480; 1874, [ii], **8**, 316).

(2) *Nitramines.*

In this group of compounds the nitro-group is attached to nitrogen. They are represented by the general formula $RR'N\cdot NO_2$ (where R = alkyl, aryl, or R·CO–; R = H or alkyl). Primary unsubstituted nitramines, $R\cdot NH\cdot NO_2$, have an acid reaction in water, and form salts by treatment with aqueous alkali. The alkali salts furnish secondary nitramine by the action of alkyl halides.

$$R\cdot NNa\cdot NO_2 + CH_3I \longrightarrow R(CH_3)N\cdot NO_2 + NaI$$

The secondary nitramines, by virtue of their structure, are neutral.

Preparation of p-*Tolylmethylnitramine.*—*p*-Tolylnitramine (2·5 g.) is mixed with a solution of 0·4 g. of sodium in 5 c.c. of methyl alcohol and 2·5 g. of methyl iodide dissolved in methyl alcohol. After keeping for 3 weeks at room temperature, the mixture is heated for 3 hours under reflux on a water-bath. The solvent is then distilled off, the residue extracted with dilute aqueous ammonia, and the insoluble matter crystallised from light petroleum. *p*-Tolylmethylnitramine is thus obtained, m. p. 75°—yield 0·48 g. (Pinnow, *Ber.*, 1897, **30**, 835; compare Bamberger, *ibid.*, 1894, **27**, 366).

The methylation of some nitramines has also been effected by diazomethane in ethereal solution (Heinke, *Ber.*, 1898, **31**, 1395; Degner and v. Pechmann, *ibid.*, 1897, **30**, 646).

Most nitramines either eliminate the nitro-group by treatment with concentrated sulphuric acid or undergo other changes. Thus methylnitramine or ethylnitramine yield nitrous oxide by the action of 40% sulphuric acid (Franchimont and Umbgrove, *Rec. trav. chim.*, 1898, 17, 288). In general, however, at least part of the nitro-group is liberated as nitrous or nitric acids which can be tested for in the usual way with ferrous sulphate (Thiele and Lachmann, *Annalen*, 1895, **288**, 269).

Arylnitramines undergo isomerisation under the influence of mineral acids. Thus phenylnitramine, $PhNH{\cdot}NO_2$, yields a mixture of *o*- and *p*-nitranilines; phenylmethylnitramine furnishes *o*- and *p*-nitromethylanilines; *o*-nitrophenylnitramine yields 2 : 6-dinitroaniline; β-naphthylnitramine yields α-nitro-β-naphthylamine. The change is effected by the action of concentrated sulphuric acid in acetic acid; less conveniently by boiling with dilute aqueous mineral acids or by the action of dry hydrogen chloride on an ethereal solution of the nitramine (Bamberger, *Ber.*, 1897, **30**, 1253). The migration of the nitro-group is usually accompanied by other reactions. Thus the primary arylnitramines yield some diazonium salt, probably owing to elimination of some of the nitro-group as nitrous acid. This is most marked with some of the halogen-substituted phenylnitramines. Thus 2 : 6-dibromophenylnitramine and 2 : 4-dichlorophenylnitramine furnish small yields of the corresponding diazonium salts in addition to the normal products of rearrangement by the action of sulphuric acid in acetic acid solution. Diazonium salts are also formed from 2 : 4 : 6-trichlorophenylnitramine and from 2 : 4 : 6-tribromophenylnitramine. The latter compound also yields some 2 : 6-dibromo-4-nitroaniline by the elimination of the *para*-bromine. Both nitramines also yield halogen-substituted quinone anils (Orton, *J.*, 1902, **81**, 806; Orton and A. E. Smith, *ibid.*, 1905, **87**, 389; 1907, **91**, 146).

The formation of diazonium salts is no doubt due to the liberation of the nitro-group as nitrous acid. This has been observed for some arylnitramines and aryl alkylnitramines. Thus 3 : 5-dinitro-*p*-tolyl-*n*-butylnitramine yields nitrous acid and the corresponding nitrosamine by treatment with concentrated sulphuric acid (Reilly and Hickinbottom, *J.*, 1919, **115**, 179).

(3) *Nitroso-Compounds.*

Nitroso-compounds may be conveniently divided into two groups: (*a*) the *C*-nitroso-compounds in which the nitroso-group is united to carbon; (*b*) *N*-nitroso-compounds in which the nitroso-group is attached directly to nitrogen.

(*a*) C-*Nitroso-Compounds.*

The simple nitroso-substituted paraffins generally appear to be white in the crystalline state but assume a blue colour when fused or vaporised. Thus nitroso-*tert.*-butane, $(Me)_3C{\cdot}NO$, is a white crystalline solid, melting to a blue liquid, which reverts to the original white crystalline solid on cooling. Its freshly prepared solutions in organic solvents are colourless, but they become blue more or less rapidly when kept at room temperature, but more rapidly on warming. 2-Nitroso-2-methylbutane and 2-nitroso-2 : 5-dimethylhexane behave similarly (Bamberger and Seligmann, *Ber.*, 1903, **36**, 692; Piloty and Ruff, *ibid.*, 1898, **31**, 457).

Nitrosobenzene and other nitroso-substituted aromatic hydrocarbons show an analogous behaviour. The earlier determinations of the molecular weight of aromatic nitroso-compounds (Bamberger and Rising, *Ber.*, 1901, **34**, 3878) have been recently supplemented by the measurements of Hammick (*J.*, 1931, 3105), Hammick and Illingworth (*ibid.*, 1930, 2358) and Ingold and Piggott (*ibid.*, 1924, **125**, 163). From these and other results it appears that nitrosobenzene and its homologues exist in a bimolecular form which undergoes more or less complete dissociation in solution. If both *ortho*-positions with respect to the nitroso-group are substituted, the dissociation is retarded. In these recent papers, and also in a paper by Hammick, New, and Sutton (*J.*, 1932, 742), will be found a discussion of the possible structures of dimeric nitroso-compounds.

The condensation of aromatic nitroso-compounds with primary aromatic amines to yield azo-compounds is an important reaction. Thus azobenzene is formed by reaction of nitrosobenzene with aniline (Baeyer, *Ber.*, 1874, **7**, 1639). Nuclear-substituted anilines behave similarly (C. Mills, *J.*, 1895, **67**, 928; Bamberger, *Ber.*, 1896, **29**, 102; v. Auwers and Röhrig, *ibid.*, 1897, **30**, 989; Freundler, *Bull. Soc. chim.*, 1907, [iv], **1**, 220; 1911, [iv], **9**, 657).

Preparation of Azobenzene.—A solution of 5 g. of nitrosobenzene in 15 g. of acetic acid is added to 5 g. of aniline in 10 g. of the same solvent. The reaction commences at once and the temperature gradually rises to 45°. When the condensation is complete the temperature falls and the azobenzene separates in almost quantitative yield (Mills, *loc. cit.*).

Preparation of o-*Methoxyazobenzene.*—*o*-Anisidine (5·6 g.) is added to a solution of nitrosobenzene (5 g.) in 20 c.c. of acetic acid, cooled in a bath of cold water. After the mixture has been kept for about 40 hours, it is poured into water. The crude azo-compound is precipitated together with some tarry matter. The pure azo-compound is obtained by steam distillation as an orange-red viscous oil, b. p. 195—197°/14 mm., which gradually solidifies, m. p. 40—41° (Bamberger, *Ber.*, 1900, **33**, 3190).

Condensation of nitrosobenzene with hydroxylamine proceeds in a similar manner in presence of sodium carbonate to yield a *syn.*-diazotate (Hantzsch, *Ber.*, 1905, **38**, 2056) (see p. 351).

$$\mathrm{Ph{\cdot}NO + H_2N{\cdot}OH \qquad Ph{\cdot}N{:}N{\cdot}OH}$$

Direct conversion into diazonium salts is effected by the action of nitric oxide on a chloroform solution of nitrosobenzene, benzenediazonium nitrate being formed. The action of nitrous acid on an acetic acid solution of nitrosobenzene furnishes the same product (Bamberger, *Ber.*, 1918, **51**, 634).

Reduction of nitroso-compounds in acid media by means of zinc, iron, or stannous chloride leads to the formation of amines:

(b) *N-Nitroso-Compounds.*

These are represented by the general formula $\begin{matrix}R'\\R\end{matrix}\!\!>N{\cdot}NO$, where R and R′ are hydrocarbon residues. The compounds are known as nitrosamines. Nitroso-derivatives of amides are also known, and are represented by the above general formula, where R is an acyl grouping and R′ a hydrocarbon radicle. They are known as nitrosamides. As there are important differences in the behaviour of these two classes of compounds, they are considered separately.

1. *Nitrosamines.*—In the absence of any basic or acidic substituent in the hydrocarbon radicle, nitrosamines are solids or liquids having a neutral reaction. They are in general stable to dilute aqueous alkali. Those derived from aliphatic and mixed aliphatic aromatic amines appear to have feeble basic properties. Thus, dry hydrogen chloride passed into a concentrated ethereal solution of dimethylnitrosamine yields a white crystalline hydrochloride easily decomposed into its components by water or alcohol (E. Renouf, *Ber.*, 1880, **13**, 2170). A similar type of compound from phenylmethylnitrosamine has been described by Hantzsch and Pohl (*Ber.*, 1902, **35**, 2975). Platinibromides of some aliphatic nitrosamines have been prepared (Gutbier and Rausch, *J. pr. Chem.*, 1913, [ii], **88**, 416). As such salts are almost completely hydrolysed by water, there is little tendency to salt formation with dilute aqueous acids.

The principal characteristic reactions of nitrosamines are the elimination of the nitroso-group and its reduction to $-NH_2$.

Elimination of the Nitroso-group.—Nitrosamines yield nitrous acid and the parent secondary amine when treated with concentrated sulphuric acid. This reaction is employed for the detection of nitrosamines, the free nitrous acid being detected by its reaction with phenol.

Liebermann's Test for Nitrosamines.—A small amount of the pure nitrosamine is treated with about 2 c.c. of cold concentrated sulphuric acid and then one or two crystals of phenol are added. On gently warming, a green or blue colour develops. Cautious dilution with water causes the colour to change through violet to reddish-violet, and finally to red. It becomes green or blue again on making alkaline.

This test is usually employed for the detection of secondary amines. For this purpose the suspected nitrosamine, which is produced by the action of nitrous acid, is taken up in ether. The ethereal solution is freed from all traces of nitrous acid by several washings with dilute aqueous sodium hydroxide. After a washing with water, it is dried in contact with anhydrous magnesium sulphate and a portion evaporated in a white porcelain dish. The test is then carried out as described above.

It should be noted that diphenylnitrosamine behaves in a characteristic manner with concentrated sulphuric acid in yielding a deep blue solution.

For obtaining the parent secondary amine from the nitrosamine, the use of concentrated sulphuric acid is of limited application. With aliphatic nitrosamines, the elimination of the nitroso-group is more conveniently effected by heating with concentrated hydrochloric acid. The hydrochloride of the secondary amine remains on evaporation of the excess of acid (Renouf, *Ber.*, 1880, **13**, 2170;

Geuther, *Annalen*, 1863, **128**, 151). To prevent secondary reactions due to the liberation of nitrous acid, it is frequently desirable to introduce some reagent capable of removing nitrous acid rapidly. This applies more particularly to alkyl arylnitrosamines. Stannous chloride is usually employed for this purpose (Nölting and Boasson, *Ber.*, 1877, **10**, 795). Less frequently the nitroso-group has been replaced by heating with a mixture of hydrochloric acid and an alcohol, or by the action of zinc dust and warm hydrochloric acid (Reilly and Hickinbottom, *J.*, 1918, **113**, 978). When nitro-groups are present in the aromatic nucleus it is obviously impracticable to use stannous chloride or zinc dust and hydrochloric acid if the action is to be restricted to the removal of the nitroso-group. In these circumstances, conversion of the nitrosamine to the corresponding secondary amine can be effected by heating with alcoholic or aqueous hydrochloric acid containing aniline hydrochloride. The same result may be achieved by heating the nitrosamine with phenol at 180°.

Preparation of 3 : 5-*Dinitro*-n-*butyl*-p-*toluidine from* 3 : 5-*Dinitro*-p-*tolyl*-n-*butylnitrosamine.*—The nitrosamine (2·4 g.) is heated under reflux for 8 hours with alcoholic hydrogen chloride (50 c.c.) containing aniline hydrochloride (1 g.). By evaporating the alcohol and then adding water, 3 : 5-dinitro-*n*-butyl-*p*-toluidine is obtained, yield 2·1 g.—m. p. 56—57° (Reilly and Hickinbottom, *J.*, 1919, **115**, 180; compare Pinnow, *Ber.*, 1897, **30**, 838).

Recently, E. C. S. Jones and Kenner (*J.*, 1932, 713) have described new conditions for the preparation of secondary amines from nitrosamines. The method consists in adding an excess of a solution of cuprous chloride in hydrochloric acid (35 g. of cuprous chloride in 200 c.c. of concentrated hydrochloric acid) to the nitrosamine. Nitric oxide is evolved, and the reaction is completed by gently warming. The amine is isolated by adding an excess of ammonia, and then distilling in steam or extracting with ether.

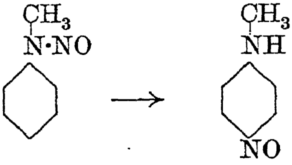
The arylnitrosamines undergo an interesting reaction in presence of dry alcoholic hydrogen chloride at room temperature. If the aryl group has the *para* position free, the nitroso-group leaves the nitrogen and enters the nucleus in the *para* position (O. Fischer and Hepp, *Ber.*, 1886, **19**, 2991; 1887, **20**, 1251; O. Fischer, *Annalen*, 1895, **286**, 156).

Preparation of p-*Nitrosomethylaniline* (X).—A saturated solution of hydrogen chloride in absolute alcohol (4 parts) is added to a solution of phenylmethylnitrosamine (IX) (1 part) in twice its volume of ether. The solution assumes a dark orange colour almost immediately. A brisk reaction sets in, heat is evolved, and crystals of *p*-nitrosomethylaniline hydrochloride separate. After keeping for some hours, the orange-red precipitate is collected and washed with ether. The free base is obtained by adding dilute sodium carbonate solution or ammonia to a cold aqueous solution of the hydrochloride. It separates from benzene as blue plate-like crystals, m. p. 118°.

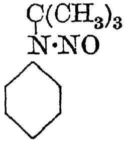
Similar conditions are used to obtain *p*-nitroso-substituted amines from other alkyl arylnitrosamines, from diarylnitrosamines, from nitrosotetrahydroquinoline, and from alkyl- and aryl-α-naphthylnitrosamines. When the nitrosamines from alkyl-β-naphthylamines are submitted to this reaction, the nitroso-group enters the α-position (Fischer and Hepp, *Ber.*, 1887, **20**, 2471; Morgan and

Evens, *J.*, 1919, **115**, 1142). A similar transformation can be brought about with the dinitrosamines of αβ-diphenylaminoethane and of βγ-diphenylaminobutanes (Morgan, Hickinbottom, and Barker, *Proc. Roy. Soc.*, *A*, 1925, **110**, 518). Instead of using alcoholic hydrogen chloride for this purpose, it is sometimes more convenient to use concentrated hydrochloric acid or a saturated solution of hydrogen chloride in acetic acid. The choice of these reagents is determined by the solubility of the salt of the nitroso-base.

Nitrosamines derived from amines containing tertiary alkyl groups behave abnormally. Thus *tert.*-butylphenylnitrosamine (XI) and the corresponding *tert.*-amyl and *tert.*-hexyl compounds do not undergo the Fischer–Hepp reaction. Solutions of hydrogen chloride in alcohol or acetic acid bring about the elimination of the nitroso-group with the formation of the hydrochloride of the secondary amine. The nitroso-group is also split out by the action of diluted sulphuric acid, but this reaction is accompanied to some extent by the elimination of the tertiary alkyl group with the formation of a diazo-compound (Hickinbottom, *J.*, 1933, 1070).



(IX.) (X.)



(XI.)

Reduction to Hydrazines.—By using mild conditions of reduction, the nitroso-group can be reduced to $-NH_2$, with the production of an asymmetrical di-substituted hydrazine.

$$RRN{\cdot}NO + 4H \qquad RRN{\cdot}NH_2 + H_2O$$

This is effected very conveniently by zinc dust and acetic acid.

Preparation of Diethylhydrazine.—150 G. of 50% aqueous acetic acid are added gradually to a mixture of 30 g. of diethylnitrosamine in 300 c.c. of water and 150 g. of zinc dust, which is stirred mechanically and maintained between 20° and 30°. After 2 hours, the reaction is completed by warming to 40—50°, further amounts of zinc and acetic acid being added if the odour of the nitrosamine still persists.

The mixture is then rendered alkaline by the addition of an excess of caustic soda and distilled over a free flame. The distillate contains varying amounts of ammonia and diethylamine as well as the hydrazine. It is neutralised with hydrochloric acid and evaporated to a syrup. The greater part of the ammonium chloride separates on cooling and is filtered off. The addition of sodium hydroxide causes the separation of diethylhydrazine and diethylamine as a colourless oil. These are distilled over or separated from the aqueous layer and converted into hydrochlorides.

The crude hydrochloride is exactly neutralised and a solution of an excess of potassium cyanate added. The mixture is then slowly raised to boiling point. If the concentration is suitable, a considerable amount of crystalline material is deposited on cooling. This is collected and crystallised from hot alcohol and then from a small amount of hot water to remove traces of potassium chloride. The product is then pure diethyl semicarbazide, m. p. 149°.

Hydrolysis of the semicarbazide with concentrated hydrochloric acid in a sealed tube at 100° yields a solution of the hydrochlorides of diethylhydrazine and ammonium. After evaporating and removing the ammonium chloride which separates, diethylhydrazine is obtained as a colourless oil by adding concentrated sodium hydroxide. It is dehydrated, first in contact with solid sodium hydroxide and then over anhydrous barium oxide. It is thus obtained as a colourless liquid, b. p. 96—99° (E. Fischer, *Annalen*, 1879, **199**, 308).

Preparation of Phenylmethylhydrazine.—Phenylmethylnitrosamine (30 g.) is mixed with 120 g. of 50% acetic acid and sufficient alcohol to make the mixture homogeneous. The solution is then added gradually to an efficiently stirred suspension of zinc dust (150 g.) in 200 c.c. of cold 90% alcohol. The rate of addition must be regulated so that the temperature does not exceed 30°; it is advisable to keep it between 10° and 20°. When reduction is complete, the mixture is heated in a water-bath and filtered hot. Sufficient caustic soda is added to the filtrate to dissolve the zinc hydroxide. It is then distilled in steam and the amine which passes over in the distillate is taken up in ether, and converted into sulphate by evaporation with dilute sulphuric acid. The distillate thus concentrated is made alkaline and the amine extracted from it by ether. After drying the ethereal solution over potassium carbonate and removing the solvent by evaporation, the crude base is treated with the calculated amount of 40% sulphuric acid, cooled to 0°, and diluted with an equal volume of absolute alcohol. The sulphate of methylphenylhydrazine separates. It is collected by filtration under suction, drained as far as possible from oily impurities, and then crystallised from hot alcohol.

The addition of an excess of alkali to an aqueous solution of the purified sulphate liberates phenylmethylhydrazine. It is taken up in ether, dried over potassium carbonate, and distilled under reduced pressure. It is collected at 131°/35 mm. as an almost colourless oil (E. Fischer, *Annalen*, 1878, **150**, 190; 1886, **236**, 198).

2. N-*Nitroso-Amides.*—The preparation of nitrosoanilides has been described on p. 221. These compounds are of interest on account of their relationship to diazo-compounds. Thus nitroso-acetanilide yields sodium *syn.*-diazotate by treatment with aqueous sodium hydroxide or with an excess of alcoholic sodium ethoxide at room temperature. Nitroso-*p*-bromoacetanilide and nitrosoacetnaphthalide behave similarly. Accordingly, these substances yield azo-compounds when treated with alkaline solutions of β-naphthol (Bamberger, *Ber.*, 1894, **27**, 915; Bamberger and J. Müller, *Annalen*, 1900, **313**, 126; Hantzsch and Wechsler, *ibid.*, 1902, **325**, 229).

$$\mathrm{Ph{\cdot}N(NO){\cdot}CO{\cdot}CH_3 + 2NaOH \longrightarrow Ph{\cdot}N{:}N{\cdot}ONa + CH_3{\cdot}CO_2Na + H_2O}$$

Nitrosoanilides appear to react directly with aniline to form diazoamino-compounds and with phenols to yield azo-compounds.

N-Nitrosomethylurethane, $\mathrm{Me{\cdot}N(NO){\cdot}CO_2Et}$, when treated with alkali, undergoes a decomposition similar in form to that shown by the nitrosoanilides. Cold concentrated potassium hydroxide yields the diazotate $\mathrm{Me{\cdot}N{:}N{\cdot}OK}$ at 0° as a white crystalline solid, which is unstable and yields diazomethane in presence of moisture. Nitrosobenzylurethane behaves similarly (Hantzsch and Lehmann, *Ber.*, 1902, **35**, 901). The decomposition of such compounds is no doubt responsible for the production of diazo-paraffins when nitrosoalkylurethanes, nitrosoalkylureas, and similar compounds are decomposed by alkali. The diazo-paraffins are prepared very conveniently by such a method.

Preparation of Diazomethane from Nitrosomethylurea.—Nitrosomethylurea (10·3 g.)—in microcrystalline form—is covered by 50 c.c. of dry ether. To this is added 70% aqueous potassium hydroxide (20 c.c.) drop by drop, a circular motion being given to the flask. After about 10 minutes, the decomposition is complete and the ethereal solution containing the diazomethane is decanted off (E. Werner, *J.*, 1919, **115**, 1096).

Phenyldiazomethane $Ph{\cdot}CH{:}N_2$, diazoethane $Me{\cdot}CH{:}N_2$, diazobutane, and diazo*iso*pentane are similarly prepared from the nitroso-derivatives of the appropriate alkylureas.

Preparation of Diazomethane from Nitrosomethylurethane.—1 Vol. of nitrosomethylurethane (1—5 c.c.) and a convenient amount of ether (30—50 c.c.) are mixed in a round-bottomed flask fitted with a condenser for distillation. Methyl alcoholic potash (1·2 vols. 25% concentration) is added and the mixture heated on the water-bath. Ether and diazomethane distil over, the operation being stopped as soon as the ether distilling over is colourless. 1 C.c. of nitrosomethylurethane gives 0·18—0·2 g. of diazomethane.

Diazoethane is prepared from nitrosoethylurethane by a similar process (v. Pechmann, *Ber.*, 1898, 31, 2643). Nitrosomethyloxamide and nitrosomethylsuccinimide furnish diazomethane by treatment with alcoholic potash (Backer, *J.*, 1912, **101**, 593).

The reduction of nitrosoanilides to acyl hydrazines apparently has not yet been accomplished. Even under mild conditions of reduction, using aluminium amalgam, sulphur dioxide, or zinc and acetic acid, the nitroso-group is eliminated with the regeneration of the original anilide. The nitroso-group is also eliminated by passing dry hydrogen chloride into a solution in benzene or chloroform, the original anilide being precipitated as hydrochloride. If alcohol or acetic acid is used as solvent, a diazonium chloride may be formed, but this reaction is not general.

Nitrosoalkylureas, however, undergo reduction to alkylhydrazines under suitable conditions (Bruning, *Annalen*, 1889, **253**, 7 ; Backer, *loc. cit.*).

TABLE XX.

Primary and Secondary Nitro-Compounds.

	B. p.	M. p.	*d.*	
Nitromethane	101°	—	$1{\cdot}138^{20}_{20}$	
Nitroethane	113	—	$1{\cdot}056^{15}_{15}$	
Nitroform	115	—	—	Colourless liquid. Yellow aq. sol. K salt gives yellow aq. sol.
sec.-Nitropropane . . .	117	—	—	
Nitropropane	131	—	$1{\cdot}008^{24}_{4}$	
Phenylnitromethane . . .	118/ 16 mm.	—	—	B. p. 226°/760 mm. (dec.). *iso*Nitro-, m. p. 84°.
p-Chlorophenylnitromethane .	—	33°	—	Oxidation → *p*-chlorobenzoic acid. *iso*Nitro-, m. p. 64°.
p-Bromophenylnitromethane .	—	60	—	Oxidation → *p*-bromobenzoic acid. *iso*Nitro-, m. p. 90°.
p-Nitrophenylnitromethane .	—	91	—	Oxidation → *p*-nitrobenzoic acid. *iso*Nitro-, m. p. 91°.
3 : 5-Dimethylphenylnitromethane.	—	47	—	*iso*Nitro-, m. p. 63°.

TABLE XXI.—*Tertiary Nitro-Compounds.*

	M. p.	B. p.	
Chloropicrin	—	112°	Piercing odour, attacks eyes and mucous. Fe and HAc → $MeNH_2$.
Tetranitromethane	—	126	Alc. KOH → K salt of nitroform.
Nitrobenzene	6°	210	HCl and Sn → aniline. *m*-Dinitrobenzene, m. p. 90°.
o-Nitrotoluene	—	222	HCl and Sn → *o*-toluidine. Aq. alkaline $KMnO_4$ → *o*-nitrobenzoic acid. 2 : 4-Dinitrotoluene, m. p. 70°.
2-Nitro-*m*-xylene	—	225	HCl and Sn → 2-amino-*m*-xylene. Trinitro-*m*-xylene, m. p. 182°; aq. $KMnO_4$ and $MgSO_4$ → 2-nitro*iso*phthalic acid, m. p. 300°.
2-Nitro-*p*-xylene	—	230	HCl and Sn → *p*-xylidine. Trinitro-*p*-xylene, m. p. 137°.
4-Nitro-*m*-xylene	—	245	HCl and Sn → 4-amino-*m*-xylene. Trinitro-*m*-xylene, m. p. 182°.
p-Nitroethylbenzene	—	241	HCl and Sn → 4-aminoethylbenzene. Trinitroethylbenzene, m. p. 37°.
o-Nitroanisole	—	265	HCl and Sn → *o*-anisidine. Dinitroanisole, m. p. 88°; trinitroanisole, m. p. 64°.
o-Nitrophenetole	—	267	HCl and Sn → *o*-phenetidine. Dinitrophenetole, m. p. 86°; trinitrophenetole, m. p. 78°.
4-Chloro-3-nitrotoluene	7	260	HCl and Sn → 4-chloro-3-aminotoluene.
m-Nitrotoluene	16	228	HCl and Sn → *m*-toluidine. Aq. alkaline $KMnO_4$ or CrO_3 and H_2SO_4 → *m*-nitrobenzoic acid.
m-Nitrobenzyl alcohol	27	—	Benzoate, m. p. 94°. Aq. alkaline $KMnO_4$ → *m*-nitrobenzoic acid.
4-Nitro-*o*-xylene	29	258	HCl and Sn → 4-amino-*o*-xylene. 3 : 4 : 6-Trinitro-*o*-xylene, m. p. 72°; 3 : 4 : 5-trinitro-*o*-xylene, m. p. 115°.
o-Chloronitrobenzene	32	246	HCl and Sn → *o*-chloroaniline. 2 : 4-Dinitrochlorobenzene, m. p. 50°; 2 : 4 : 6-trinitrochlorobenzene, m. p. 83°.
2 : 4-Dichloronitrobenzene	33	258	HCl and Sn → 2 : 4-dichloroaniline.
4-Bromo-3-nitrotoluene	33	—	HCl and Sn → 4-bromo-*m*-toluidine.
4-Chloro-1 : 2-nitrobenzene	36	—	Boiling aqueous alkali → 2-nitro-5-chlorophenol.
2 : 4 : 6-Trinitroethylbenzene	37	—	Aq. alcoholic KOH → red coloration.
4-Chloro-2-nitrotoluene	38	240	HCl and Sn → 4-chloro-2-aminotoluene. Aq. alkaline $KMnO_4$ → 4-chloro-2-nitrobenzoic acid.
o-Bromonitrobenzene	41	259	HCl and Sn → *o*-bromaniline. 2 : 4-Dinitrobromobenzene, m. p. 72°; 2 : 4 : 6-trinitrobromobenzene, m. p. 123°.
Nitromesitylene	44	255	HCl and Sn → mesidine. 2 : 4-Dinitromesitylene, m. p. 86°; 2 : 4 : 6-trinitromesitylene, m. p. 235°.
4-Bromo-2-nitrotoluene	46	256	
m-Chloronitrobenzene	45	236	HCl and Sn → *m*-chloraniline. 4-Chloro-1 : 2-dinitrobenzene, m. p. 36°.
o-Nitrobenzyl chloride	49	—	Boiling aq. Na_2CO_3 → *o*-nitrobenzyl alc. Aq. alkaline $KMnO_4$ → *o*-nitrobenzoic acid.
o-Nitroiodobenzene	49	288	Fe and HAc or $FeSO_4$ and aq. NH_3 → *o*-iodoaniline. $NO_2C_6H_4{\cdot}ICl_2$, *ca.* 96° dec.; $NO_2C_6H_4IO$, *ca.* 100° dec.
2 : 5-Dinitrotoluene	50	—	Boiling dil. HNO_3 → 2 : 5-dinitrobenzoic acid.
2 : 4-Dinitrochlorobenzene	50	—	Boiling aq. Na_2CO_3 → 2 : 4-dinitrophenol. Reaction with amines, see p. 271. 2 : 4 : 6-Trinitrochlorobenzene, m. p. 83°. (J.), red-lilac.
m-Nitrobromobenzene	56	251	HCl and Sn → *m*-bromaniline.
p-Nitrotoluene	54	238	HCl and Sn → *p*-toluidine. 2 : 4-Dinitrotoluene, m. p. 60°. Aq. alkaline $KMnO_4$ or CrO_4 and H_2SO_4 → *p*-nitrobenzoic acid.
p-Nitroanisole	54	—	HCl and Sn → *p*-anisidine. 2 : 4-Dinitroanisole, m. p. 88°; 2 : 4 : 6-trinitroanisole, m. p. 64°.
2 : 6-Dinitro-*p*-cymene	54	—	Trinitro-*p*-cymene, m. p. 118°.
2 : 5-Dichloronitrobenzene	55	266	HCl and Sn → 2 : 5-dichloraniline.
2 : 6-Dinitrotoluene	60	—	Boiling dil. HNO_3 → 2 : 6-dinitrobenzoic acid. (J.), no coloration.
p-Nitrophenetole	60	—	HCl and Sn → *p*-phenetidine. 2 : 4-Dinitrophenetole, m. p. 86°; 2 : 4 : 6-trinitrophenetole, m. p. 78°.
α-Nitronaphthalene	61	304	HCl and Sn → *α*-naphthylamine. 1 : 5-Dinitronaphthalene, m. p. 216°; 1 : 8-dinitronaphthalene, m. p. 170°. H_2SO_4 → red colour.
2 : 4 : 6-Trinitroanisole	64	—	Alcoholic NH_3 → picramide; aq. KOH → picric acid.
2 : 4 : 6-Trichloronitrobenzene	68	—	
2 : 4-Dinitrotoluene	70	—	HCl and Sn → *m*-toluylenediamine; CrO_3 and H_2SO_4 → 2 : 4-dinitrobenzoic acid; calc. amount of $SnCl_2$ in alc. HCl → 4-nitro-*o*-toluidine. (J.), blue.
5-Nitro-*ψ*-cumene	71	265	HCl and Sn → 5-amino-*ψ*-cumene. Trinitro-*ψ*-cumene, m. p. 185°. CrO_3 and HAc → 5-nitrobenzenetricarboxylic acid.
p-Nitrobenzyl chloride	71	—	Boiling aq. Na_2CO_3 → *p*-nitrobenzyl alcohol, m. p. 93°. Aq. alkaline $KMnO_4$ → *p*-nitrobenzoic acid; KI → *p*-nitrobenzyliodide; Zn and HCl → *p*-toluidine.
2 : 4-Dinitrobromobenzene	72	—	Boiling aq. Na_2CO_3 → 2 : 4-dinitrophenol. Reaction with amines, see p. 271.

3 : 4 : 6-Trinitro-*o*-xylene	72	—	
o-Nitrobenzyl alcohol	74	—	Acetate, m. p. 35°. Oxidation → *o*-nitrobenzaldehyde → *o*-nitrobenzoic acid.
5-Nitro-*m*-xylene	75	273	Sn and HCl → 5-amino-*m*-xylene. 4 : 5 : 6-Trinitro-*m*-xylene, m. p. 125°, and some 2 : 5 : 6-trinitro-*m*-xylene, m. p. 90°.
3 : 5-Dinitro-*o*-xylene	76	—	3 : 4 : 5-Trinitro-*o*-xylene, m. p. 115°, and 3 : 4 : 6-trinitro-*o*-xylene, m. p. 72°.
Trinitrophenetole	78	—	
β-Nitronaphthalene	79	—	Zn and HAc → β-naphthylamine.
2 : 4 : 6-Trinitrotoluene	81	—	Oxidation, see p. 34. Benzaldehyde → 2 : 4 : 6-trinitrostilbene, m. p. 156° (Ullmann and Gschwind, *Ber.*, 1908, **41**, 2297). (J.), red.
2 : 4-Dinitro-*m*-xylene	82	—	Alc. $(NH_4)_2S_x$ → 2-nitro-4-amino-*m*-xylene.
p-Nitrochlorobenzene	83	234	HCl and Sn → *p*-chloraniline. 2 : 4-Dinitrochlorobenzene, m. p. 50°; 2 : 4 : 6-trinitrochlorobenzene, m. p. 83°.
2 : 4 : 6-Trinitrochlorobenzene	83	—	Warm aq. alkali → picric acid; NaOMe in MeOH → trinitroanisole; aniline → 2 : 4 : 6-trinitrodiphenylamine. (J.), blood red.
2 : 5-Dibromonitrobenzene	85	—	HCl and Sn → 2 : 5-dibromoaniline.
2 : 4-Dinitromesitylene	86	—	
m-Dinitrobenzene	90	297	Alc. $(NH_4)_2S_x$ → *m*-nitraniline; Fe and HAc or Sn and HCl → *m*-phenylenediamine. (J.), violet-red.
4 : 6-Dinitro-*m*-xylene	93	—	Trinitro-*m*-xylene, m. p. 182°.
2 : 3-Dinitro-*p*-xylene	93	—	
p-Nitrobenzyl alcohol	93	185°/ 12 mm.	Acetate, m. p. 78°. Alkaline $KMnO_4$ → *p*-nitrobenzoic acid.
3 : 5-Dinitrotoluene	93	—	CrO_3 and H_2SO_4 → 3 : 5-dinitrobenzoic acid; alcoholic $(NH_4)_2S$ → 3-nitro-5-aminotoluene.
2 : 4 : 5-Tribromonitrobenzene	94	—	HCl and Sn → 2 : 4 : 5-tribromoaniline.
2 : 4 : 6-Trinitro-3-*tert.*-butyltoluene	96	—	Musk odour.
2 : 4 : 6-Trinitrocumene	109	—	
Trinitro-*tert.*-butylbenzene	109	—	Musk odour.
2 : 4 : 6-Trinitro-1 : 3-dimethyl-5-*tert.*-butylbenzene	110	—	Musk odour.
4-Nitrodiphenyl	113	—	Sn and HCl → 4-aminodiphenyl; CrO_3 in HAc → *p*-nitrobenzoic acid.
4 : 5-Dinitro-*o*-xylene	115	—	3 : 4 : 5-Trinitro-*o*-xylene, m. p. 115°.
2 : 3 : 6-Trinitro-*p*-cymene	118	—	
1 : 3 : 5-Trinitrobenzene	122	—	Addition comps. with arylamines. $K_3Fe(CN)_6$ in warm aq. Na_2CO_3 → picric acid (Hepp, *Annalen*, 1882, **215**, 353). (J.), blood-red.
2 : 6-Dinitro-*p*-xylene	123	—	
2 : 4 : 6-Tribromonitrobenzene	125	—	HCl and Sn → 2 : 4 : 6-tribromaniline.
p-Bromonitrobenzene	126	254	HCl and Sn → *p*-bromaniline. 2 : 4-Dinitrobromobenzene.
2 : 4 : 6-Trichloro-1 : 3-dinitrobenzene	130	—	
2 : 4 : 5-Tribromo-1 : 3-dinitrobenzene	135	—	HCl and Sn → 5-bromo-1 : 3-diaminobenzene.
2 : 3 : 5-Trinitro-*p*-xylene	137	—	Alcoholic NH_3 at 100° → 3 : 5-dinitro-1 : 4-dimethyl-2-aminobenzene.
2 : 5-Dinitro-*p*-xylene	147	—	
2 : 4 : 2′ : 4′-Tetranitrodiphenyl	163	—	
1 : 8-Dinitronaphthalene	168	—	
p-Dinitrobenzene	171	—	Sn and HCl → *p*-phenylenediamine. Boiling alc. KOH → *p*-nitrophenetole. Prolonged action of boiling aq. NaOH → *p*-nitrophenol. (J.), no coloration.
2 : 4 : 2′ : 4′-Tetranitrodiphenylmethane	172	—	CrO_3 in HAc → tetranitrobenzophenone, m. p. 172°.
p-Iodonitrobenzene	174	—	Zn dust and H_2O or $FeSO_4$ and aq. NH_3 → *p*-iodoaniline. $NO_2C_6H_4ICl_2$, dec. indef.
2 : 4 : 6-Trinitro-*m*-xylene	182	—	
3 : 5 : 6-Trinitro-ψ-cumene	185	—	A drop of NaOH to alcoholic soln. → intense green coloration.
4 : 4′-Dinitrodiphenylmethane	183	—	HCl and Sn → diaminodiphenylmethane; CrO_3 in HAc → 4 : 4′-dinitrobenzophenone, m. p. 189°.
2 : 4 : 6-Tribromo-1 : 3-dinitrobenzene	192	—	Zn and HAc → tribromo-*m*-phenylenediamine; HCl and Sn → *m*-phenylenediamine.
1 : 5-Dinitronaphthalene	216	—	Alc. $(NH_4)_2S$ → 5-nitro-α-naphthylamine at room temp.; → 1 : 5-diaminonaphthalene on heating. Fairly stable to oxidation.
4 : 4′-Dinitrodiphenyl	232	—	HCl and Sn → benzidine. Stable to CrO_3 in HAc.
Trinitromesitylene	235	—	No coloration with alc. KOH or alc. NH_3.

CHAPTER IX

AZO- AND DIAZO-COMPOUNDS

(1) Diazo-Compounds.
  (*a*) Aromatic Diazonium Compounds.
    1. Replacement of the Diazo-Group by Hydrogen.
    2. Replacement of the Diazo-Group by Hydroxyl.
    3. Replacement of the Diazo-Group by Halogen, –CN, –CNS, or Triazo-Groups.
    4. Replacement of the Diazo-Group by other Groups.
      (*a*) Aryl.
      (*b*) Nitro-.
      (*c*) Sulphinic.
      (*d*) Preparation of Aryl-arsinic and -stibinic Acids.
      (*e*) Thiol, Sulphide and Disulphide.
    5. Action of Alkalis : Formation of Diazotates.
    6. Reaction with Amines.
      (*a*) Formation of Diazoamino-Compounds.
      (*b*) Formation of Aminaozo-Compounds.
    7. Reaction with Phenols.
    8. Reduction of Diazo-Compounds. Formation of Aryl Hydrazines.
  (*b*) Aliphatic Diazo-Compounds.
(2) Azo-Compounds.
    1. Oxidation of Azo-Compounds.
    2. Fission of Azo-Compounds.

(1) *Diazo-Compounds.*

In its widest interpretation, the term diazo-compound includes aliphatic compounds of the general formula $R\cdot CHN_2$ and those in which one of the nitrogen of the diazo-group is joined to an aryl or heterocyclic nucleus with unsaturated valencies. These latter compounds are represented by the general formula $R\cdot N_2X$. It is proposed to treat the two classes separately.

(a) *Aromatic Diazonium Compounds.*

The action of nitrous acid on cold aqueous solutions of aniline and its homologues in a moderate excess of dilute mineral acid results in the formation of diazonium salts, the chlorides of which have the general formula

$R\cdot\overset{\overset{N}{\vdots}}{N}\cdot Cl\cdot$

Such salts can be isolated in a crystalline state by suitable methods. In general, they are crystalline solids, insoluble in ether and more or less freely soluble in water. In aqueous solution, the chlorides and nitrates have a neutral reaction and are ionised to approximately the same extent as the corresponding ammonium salts. Solutions of the diazonium chlorides or sulphates give the ordinary ionic tests for the chloride or sulphate ion. By double decomposition the anion may be displaced by others provided that the solubility relationships are favourable. Sparingly soluble chromates, ferrocyanides, picrates, and tungstates have thus been prepared (Baeyer and C. Jaeger, *Ber.*, 1875, **8**, 894; Griess, *ibid.*, 1879, **12**, 2119; Meldola and Eynon, *J.*, 1905, **87**, 4; Caro and Griess, *Jahresb.*, 1867, 915). Morgan and Micklethwait (*J.*, 1905, **87**, 933) have succeeded in preparing a crystalline carbonate and nitrite by this means from benzoyl-*p*-aminobenzenediazonium chloride. The action of potassium cyanide and of sulphites on diazonium salts is abnormal (see p. 351). A large number of diazonium platinichlorides and aurichlorides have been prepared by the addition of chloroplatinic acid or aurichloric acid to the diazonium salt. In addition, a number of other double salts from benzenediazonium salts and their homologues are known, such as the stannochloride, B_2SnCl_4, mercurochloride, $B,HgCl_3$, argentocyanide $B,Ag(CN)_2$ (Griess, *Ber.*, 1885, **18**, 965; Hantzsch and Danziger, *ibid.*, 1897, **30**, 2529). Diazonium halides yield polyhalide salts having, at least, a formal resemblance to the ammonium periodides (compare, however, Chattaway, *J.*, 1915, **107**, 105). Thus benzenediazonium chloride or bromide yields the perbromide $Ph{\cdot}N_2{\cdot}BrBr_2$ by treatment with bromine water (Griess, *Annalen*, 1866, **137**, 50). A number of other perhalides such as $PhN_2{\cdot}ClI_2$, $PhN_2{\cdot}ICl_2$, $PhN_2{\cdot}IBr_2$, etc., have been described by Hantzsch (*Ber.*, 1895, **28**, 2754). Evidently diazonium compounds, in so far as they are salts, resemble the ammonium and quaternary ammonium salts. The resemblance to quaternary ammonium salts is strengthened by the formation of strongly alkaline solutions of the diazonium hydroxide when diazonium chlorides are treated with moist silver oxide. These hydroxides are not sufficiently stable to be isolated, but measurements on the aqueous solutions have shown that they are strong bases with affinity constants intermediate between those of the caustic alkalis and ammonia (Davidson and Hantzsch, *Ber.*, 1896, **31**, 1612). They yield diazonium salts by neutralisation with acids and can be titrated accurately with standard acid using methyl-orange as indicator.

Preparation of Benzenediazonium Perbromide.—A mixture of 5 g. of aniline, 15 g. of concentrated hydrochloric acid, and 30 g. of crushed ice is diazotised by the addition of approximately 5 g. of sodium nitrite in 15 c.c. of water. The diazotisation is complete when the solution gives an immediate and permanent blue coloration with starch iodide paper. The temperature is kept at 0° throughout the operation.

The solution of the diazonium salt is stirred mechanically, cooled by an external freezing mixture, and a solution of 14·9 g. of bromine and 8·9 g. of potassium bromide in 17·8 c.c. of water is added.

The perbromide separates in a crystalline form. It is washed with water, collected by filtration, and washed on the funnel with a little alcohol and then ether.

It is dried at a temperature not exceeding 40° and is kept in a vacuum desiccator in the dark (Bülow and Schmachtenberg, *Ber.*, 1908, **41**, 2607).

Diazonium salts are, in general, unstable compounds, and many decompose in aqueous solution at temperatures above 5°. In the dry state many of them are explosive, a property which appears to be enhanced by the presence of suitable anions. Thus benzenediazonium nitrate is very sensitive to shock, and explodes with extreme violence when heated. Diazonium picrates and chromates are also very sensitive, and explode violently. Indeed, the use of diazonium chromates as explosives has been patented (F.P. 73,826). Benzenediazonium perchlorate is stated to explode on rubbing, even when moist (Vorländer, *Ber.*, 1906, **39**, 2714).

The most important reactions of diazonium salts are those involving the diazonium group. By choosing suitable conditions, the diazonium group can be replaced by a very large variety of other groups such as –Br, –Cl, –I, –CN, –CNS, –CNO, –aryl, $-NO_2$, etc. This therefore provides a general method for the preparation of substituted derivatives of the aromatic hydrocarbons. It is also possible to reduce the diazonium group to obtain aryl hydrazines; to bring about reaction with amines and phenols with the formation of substituted azo-compounds; and to oxidise the diazo-compound to nitramine.

Replacement of the Diazonium Group. (1) *By Hydrogen*.—One of the earliest methods to be used for the replacement of the diazonium group by hydrogen consisted in boiling with alcohol (Griess, *Annalen*, 1866, **137**, 67; *J.*, 1865, **18**, 315; 1867, **20**, 54). This reaction was later shown to furnish a greater or smaller proportion of alkyl aryl ethers. Thus benzenediazonium sulphate yields 70% of anisole and some benzene when boiled with methyl alcohol (Hantzsch and Jochem, *Ber.*, 1901, **34**, 3337). The reaction between diazonium salts and alcohols therefore takes place in two directions:

$$\begin{tikzcd} & PhH + N_2 + HCl + C_2H_4O \\ Ph\cdot N_2Cl + C_2H_5\cdot OH \arrow[ur] \arrow[dr] & \\ & PhOEt + HCl + N_2 \end{tikzcd}$$

It is evident from several careful investigations on the conditions governing these reactions that the principal factors which determine the relative proportions of the two products are the nature of the substituents in the aromatic nucleus and the alcohol. In general, methyl alcohol yields a greater proportion of the ether than its homologues. As far as the lower aliphatic alcohols are concerned, the proportion of ether in the product diminishes with increase in the molecular weight of the alcohol. Thus while benzenediazonium sulphate furnishes a 60% yield of ether on boiling with ethyl alcohol, only a 50% yield is obtained with propyl alcohol; fermentation amyl alcohol gives but 30% yield of ether. The presence of halogens, nitro-groups, or carboxyl as substituents in the aromatic nucleus favours the replacement of the diazonium group by hydrogen at the expense of ether formation. This fact is particularly useful, since it provides a general method for eliminating the diazonium grouping when nitro-groups are also present, as the other methods available cannot be used without reducing the nitro-group (Remsen, *Ber.*, 1885, **18**, 65; Remsen and Palmer, *Amer. Chem. J.*, 1886, **8**, 243; Cameron, 1898, **20**, 229; Hantzsch and Jochem, *loc. cit.*; Hantzsch and Vock, *Ber.*, 1903, **36**, 2061).

Preparation of m-*Nitrotoluene.*—A mixture of 100 g. of ethyl alcohol, 34 g. of 3-nitro-4-aminotoluene, and 50 g. of concentrated sulphuric acid is cooled below 10° by an external bath of ice. While mechanically stirred, a concentrated aqueous solution of 17 g. of sodium nitrite is added slowly, the temperature being kept below 10°. When diazotisation is complete, the solution is heated very gently under reflux till the evolution of nitrogen ceases. As much of the alcohol and acetaldehyde as possible is then distilled off through a fractionating column and the residue distilled in steam. The oil in the distillate is separated with the aid of ether, the ethereal solution washed with dilute alkali, then with water, and dried in contact with calcium chloride. It is finally fractionated under reduced pressure. *m*-Nitrotoluene is collected at 113—114°/15 mm.—yield about 18—20 g. (Clarke and Taylor, *Organic Syntheses*, 1923, **3**, 91).

The addition of alkali, sodium alkoxides, or zinc dust to the alcoholic solution of the diazonium salt favours the replacement of the diazonium group by hydrogen. This reaction also appears to yield a noticeable proportion of diphenyl (Beeson, *Amer. Chem. J.*, 1894, **16**, 235).

Replacement of the diazonium group by hydrogen can be effected by other methods, such as the use of alkaline stannite (Friedländer, *Ber.*, 1889, **22**, 587), or by the action of hypophosphorus acid (Mai, *ibid.*, 1902, **35**, 162; compare Bertheim, *ibid.*, 1908, **41**, 1855; Stoermer and Heymann, *ibid.*, 1912, **45**, 3103).

Preparation of Benzene from Benzenediazonium Chloride.—An aqueous solution of benzenediazonium chloride is added to an excess of aqueous sodium hydroxide solution mixed with crushed ice. To this is added a solution of stannous chloride in an excess of aqueous caustic soda. Nitrogen is evolved at room temperature and a layer of benzene separates which is removed by distillation in steam.

Diazotised α-naphthylamine yields naphthalene under similar conditions.

Preparation of Toluene from p-*Toluenediazonium Chloride.*—A mixture of 8 g. of *p*-toluidine, 20 c.c. of concentrated hydrochloric acid, and 50 c.c. of water is diazotised with the usual precautions and the solution added to 40 c.c. of hypophosphorous acid. The mixture is kept at 0°. After several days the coloured liquid which has separated on the surface is removed, washed with dilute aqueous alkali, and distilled. 4·5 G. of pure toluene are obtained.

Under similar conditions diazotised aniline yields benzene and some diphenyl.

Preparation of Diphenyl.—Benzidine (3 g.), 7 c.c. of concentrated hydrochloric acid, and 40 c.c. of water are heated together, then cooled and diazotised. The diazonium solution is mixed with hypophosphorous acid (from 15 g. of Ca salt) and kept at 0°. The crude diphenyl, which separates, is collected, washed with dilute alkali, and then steam distilled—yield 1·5 g.

A less direct method consists in reduction of the diazonium salt to the hydrazine and subsequent oxidation with Fehling's solution.

(2) *Replacement by* –OH.—Benzenediazonium sulphate yields phenol when its aqueous solution is heated (Griess, *J.*, 1867, **20**, 41, 53). Its homologues behave similarly.

$$C_6H_5{\cdot}N_2{\cdot}HSO_4 + H_2O \longrightarrow C_6H_5OH + H_2SO_4 + N_2$$

In the preparation of phenols by this process it is advisable to use the diazonium sulphate rather than the chloride or nitrate, which, although decomposing in the direction indicated above, usually give other products as well. The chloride in presence of the excess of hydrochloric acid used for the diazotisation gives a noticeable amount of chloro-compound, while the nitrate furnishes serious amounts of nitrophenols. The method is illustrated by the following.

Preparation of p-*Cresol.*—*p*-Toluidine (20 g.) is warmed with concentrated sulphuric acid (25 g.) diluted with 600 c.c. of water. The resulting solution is cooled in ice and a solution of sodium nitrite (14·5 g.) is added gradually. Towards the end of the diazotisation, the solution must be tested after each addition of nitrite for the presence of free nitrous acid. When there is a distinct positive reaction with starch iodide paper, the diazotisation is complete. The slight excess of the nitrous acid is then removed by adding urea, and the solution is heated under reflux in a water-bath till there is no further effervescence. The solution is then steam distilled till no more *p*-cresol passes over. The distillate is then saturated with salt and extracted several times with ether. After drying the ethereal solution in contact with anhydrous magnesium sulphate, the solvent is removed and the residue distilled. *p*-Cresol is collected between 195° and 200° and solidifies on nucleating, m. p. 35—36°—yield 8—11 g.

Preparation of m-*Bromophenol.*—*m*-Bromaniline (200 g.) is dissolved in 2,000 c.c. of methyl alcohol and the solution cooled to 0°. Concentrated sulphuric acid (130 c.c.) is added, the first half quite slowly, the rest more rapidly. Amyl nitrite (152 g.) is then added to the clear solution. The diazonium sulphate soon commences to separate, and after 1 hour the separation is complete. It is necessary during the diazotisation that the temperature should not rise above 25°. The mixture must therefore be cooled in ice-water.

The diazonium sulphate is collected by filtration, washed with alcohol and ether, and then dissolved in 3 l. of water. The solution, after filtering, is kept at 40—45° for 5 hours. Some of the *m*-bromophenol rises to the surface as an oil, which is removed. The remainder is obtained by saturating the aqueous solution with sodium sulphate and then extracting with ether. After drying the crude product with anhydrous magnesium sulphate, pure *m*-bromophenol is collected at 135—140°/12 mm.—yield 44 g. (Diels and Bunzl, *Ber.*, 1905, **38**, 1495).

Preparation of m-*Nitrophenol.*—Cold diluted sulphuric acid (from 90 c.c. water and 66 c.c. of concentrated sulphuric acid) is added to *m*-nitraniline (42 g.) while the mixture is stirred mechanically. Thereafter, 160 g. of crushed ice are added. When an homogeneous mixture is obtained, the amine is diazotised by the rapid addition of 21 g. of sodium nitrite in 50 c.c. of water, the temperature being kept at 0—5° throughout the operation. The completion of the diazotisation is recognised by testing with starch iodide paper, till one drop of the solution gives a distinct blue colour. A precipitate of *m*-nitrobenzenediazonium sulphate separates. It is allowed to settle and the supernatant solution added from a dropping funnel to a mixture of 200 c.c. of concentrated sulphuric acid and 150 c.c. of water at such a rate that the solution boils vigorously. When all the diazonium solution has been added, the moist solid diazonium sulphate is added a little at a time and at such a rate that there is no excessive foaming. When all the diazonium salt has been added, the mixture is boiled vigorously for a few minutes, and then, while being stirred mechanically, it is cooled rapidly.

m-Nitrophenol separates as a crystalline magma, which is collected by filtration, thoroughly drained from the mother-liquor, and washed with several amounts of ice-water. In all about 100 c.c. of water are used. The nitrophenol is then dried by spreading on large sheets of filter-paper in a warm room—yield about 35 g.

It is purified by dissolving it in hot hydrochloric acid (1 : 1), filtering and then cooling. *m*-Nitrophenol separates as light yellow crystals, m. p. 96°. Alternatively it may be purified by distillation under reduced pressure. This method is more convenient when working with large amounts of material (Manske, *Organic Syntheses*, 1928, **8**, 80; compare Adams and Wilson, *ibid.*, 1923, **3**, 87; Henriques, *Annalen*, 1882, **215**, 323; Bantlin, *Ber.*, 1878, **11**, 2100).

The success of this type of preparation depends on the stability of the diazonium salt in aqueous solution. Those derived from aniline and its homologues decompose fairly readily to furnish the phenol. The presence of nitro- and halogen groups in the aromatic nucleus appears in general to enhance the stability of the diazonium group. Thus 2 : 4 : 6-trichlorobenzene diazonium chloride may be boiled with water without any phenol being formed (Hantzsch, *Ber.*, 1895, **28**, 685). 2 : 4 : 6-Trobromobenzenediazonium sulphate behaves similarly (Silberstein, *J. pr. Chem.*, 1883, [ii], **27**, 105; Hantzsch, *Ber.*, 1900, **33**, 2519; compare Cain and Norman, *J.*, 1906, **89**, 19; Orton, *P.*, 1905, **21**, 170). Outstanding examples of stable diazonium salts are found among those derived from amino-anthraquinones, which may be recrystallised from boiling water.

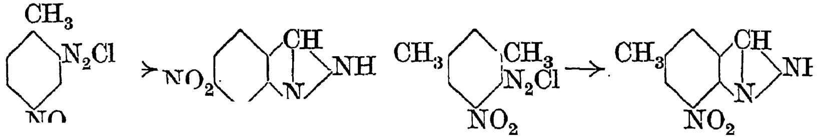
A further complication in the formation of phenols by this method is that some diazo-compounds which are comparatively stable may actually couple with the phenol as it is formed. As an example of this we have the formation of α-naphthol-4-sulphonic acid from naphthionic acid by the diazo-reaction. The product is contaminated, however, with a small amount of the azo-compound.

A modification of the usual process for replacing the diazonium group in comparatively stable compounds has been used by Heinichen (*Annalen*, 1889, **253**, 281), with the object of overcoming some of these difficulties. It consists in heating the concentrated diazonium salt solution with sulphuric acid of such a strength that the mixture boils at 150°. Although this process gives satisfactory results in some cases (*e.g.* with 2 : 6-dibromobenzene diazonium salts), it fails with many of the more stable salts, doubtless owing to the fact that the excess of moderately concentrated sulphuric acid stabilises the diazonium salt. A more satisfactory method consists in adding the diazonium solution to a mixture of dilute sulphuric acid and sodium sulphate heated to 135—145° (Kalle & Co., E.P. 7233/1897; D.R.-P. 95,339).

Preparation of Guaiacol from Diazotised o-*Anisidine.*—The diazonium solution is prepared in the usual way from 22 g. of *o*-anisidine, 48 g. of 50% sulphuric acid, 140 c.c. of water, and a solution of 14 g. of sodium nitrite in 45 c.c. of water. It is added from a dropping funnel to a mixture of 140 g. of anhydrous sodium sulphate, 195 g. of concentrated sulphuric acid, and 106 c.c. of water contained in a distillation flask fitted with a condenser and heated in an oil-bath at 135—145°. The distillate consists of water containing part of the guaiacol suspended in it, the rest in solution. The total distillate is saturated with ammonium chloride and extracted with ether. After drying the solution in contact with magnesium sulphate, the solvent is evaporated and the residue fractionated. Guaiacol is collected at 200—205°, m. p. 33°.

Trichloro- and tribromo-phenols are obtained, although in small yield, by decomposition of the appropriate diazonium salts under similar conditions. The method has also been applied successfully to the preparation of 2 : 5-dichlorophenol, 2 : 4-dibromophenol, 3-chloro-*p*-cresol, 3-bromo-*p*-cresol, and 3 : 5-dibromo-*p*-cresol from the corresponding diazonium salts (Cain and Norman, *J.*, 1906, **89**, 19).

Another type of decomposition may occur with diazonium salts having a methyl group *ortho* to the diazonium group. Thus, by gently warming diazotised 4-nitro-*o*-toluidine, a mixture of 4-nitro-*o*-cresol and 4-nitroindazole is obtained (Witt, Nölting, and Grandmougin, *Ber.*, 1890, **23**, 3635; Michel and Grandmougin, *ibid.*, 1893, **26**, 2349). Diazonium salts from 5-nitro-4-amino-*m*-xylene behave similarly (Gabriel and Stelzner, *Ber.*, 1896, **29**, 303). A parallel reaction has been observed when the diazonium compounds from mesidine, *o*-toluidine, or 4-amino-*m*-xylene are treated with dilute aqueous alkali (Bamberger, *Annalen*, 1899, **305**, 289), but under these conditions some of the product is an azo-compound derived by coupling of the diazonium compound with the indazole already formed.



Preparation of 4-*Nitroindazole.*—A solution of 4-nitro-*o*-toluidine (30 g.) in 60 g. of concentrated sulphuric acid diluted with 1000 c.c. of water is cooled and diazotised with 14 g. of sodium nitrite. The solution is then gently warmed on a water-bath so that there is only a very slow evolution of nitrogen. It is finally heated to boiling point and filtered through a folded filter.

The clear pale yellow solution becomes turbid on cooling and the reaction product separates as oily drops, which solidify to a paste of yellow needles. The paste is filtered off, and a further small amount can be obtained by concentrating the filtrate. The solid is a mixture of 4-nitro-*o*-cresol and 4-nitroindazole. It is best separated by dissolving 15 g. of the mixture in 300 c.c. of hot water containing 10 c.c. of 30% sodium hydroxide solution. The hot solution is filtered, cooled to room temperature, and then saturated with carbon dioxide. Almost pure nitro-indazole separates. It crystallises from hot water in white needles, m. p. 181° (Witt, Nölting, and Grandmougin, *loc. cit.*; Michel and Grandmougin, *loc. cit.*).

Preparation of 3-*Methyl*-5-*nitroindazole.*—4-Amino-5-nitro-*m*-xylene (10 g.) is dissolved in 50 c.c. of concentrated sulphuric acid and poured with stirring into 2 l. of water. After cooling, it is diazotised by 10 g. of sodium nitrite in 100 c.c. of water. The precipitate gradually dissolves and the solution is heated gently on a water-bath for 2½ hours. The tarry matter which separates is removed by filtering the boiling solution through glass-wool. The nitromethylindazole separates out, on cooling, as a bright yellow crystalline precipitate. A further small amount may be obtained by extraction of the tar with boiling water—yield 5 g. The indazole crystallises from boiling alcohol as light yellow needles, m. p. 192—193° (Gabriel and Stelzner, *loc. cit.*)

(3) *Replacement by Halogen, –CN, –CNS, –CNO, or Triazo-Group.*—Diazonium chlorides, when warmed with an excess of fuming or concentrated hydrochloric acid, furnish some of the corre-

sponding chloro-substituted hydrocarbon, the reaction being accompanied by the formation of the phenol.

$$Ph{\cdot}N_2Cl \longrightarrow PhCl + N_2$$

In hydrobromic acid, the diazonium bromide behaves similarly (Griess, *Ber.*, 1885, **18**, 961; Gasiorowski and Waÿss, *ibid.*, p. 337; Hübner and Mejert, *ibid.*, 1875, **6**, 794). The reaction is, however, not generally employed in this form for the replacement of the diazonium group by –Cl or –Br, as more efficient methods are available. The method, however, succeeds well for the preparation of iodo-derivatives, the replacement of the diazonium group taking place when sodium iodide is added to a solution of diazonium salt containing an excess of mineral acid.

Preparation of Iodobenzene.—Aniline (25 g.) is warmed with concentrated sulphuric acid (30 c.c.) diluted with 250 c.c. of water and the resulting solution cooled to 0° while it is stirred mechanically. It is diazotised by the gradual addition of a solution of 19 g. of sodium nitrite in water, the reaction mixture being tested for free nitrous acid at intervals towards the end of the diazotisation. When the operation is complete, the excess of nitrous acid is removed by the addition of urea, and a concentrated aqueous solution of 60 g. of potassium iodide added. After keeping at room temperature for several hours, the mixture is warmed under reflux to complete the reaction and then steam distilled. Crude iodobenzene passes over as an oil, which, after taking up in ether, is washed with aqueous alkali and then water. It is finally dried and distilled, b. p. 188°—yield 35—45 g.

The introduction of the triazo-group is effected by adding sodium azide to an acid solution of the diazonium salt (Nölting and Michel, *Ber.*, 1893, **26**, 86). This method has been used for the preparation of mono-, di-, and tri-triazo-substituted aromatic hydrocarbons.

Preparation of α-Triazonaphthalene.—A solution of 30 g. of α-naphthylamine in 180 c.c. of glacial acetic acid is mixed with 80 c.c. of concentrated sulphuric acid and diazotised by the addition of an aqueous solution of 15 g. of sodium nitrite, the usual precautions being taken. When the diazotisation is complete, the slight excess of nitrous acid is removed by the addition of 5 g. of powdered urea, and then a solution of 15 g. of sodium azide in 50 c.c. of water is added. The solution becomes turbid and nitrogen is evolved. After keeping for several hours at 0°, the oil, which has separated, is taken up in ether and distilled in steam. α-Triazonaphthalene, which slowly distils over, is dissolved in ether, the ethereal solution washed with hydrochloric acid and then with 20% aqueous potash, and dried in contact with calcium chloride. Evaporation of the ether leaves the pure triazo-compound, m. p. 12°; it decomposes on distillation (Forster and Fierz, *J.*, 1907, **91**, 1945).

Preparation of m*-Bistriazobenzene.*—*m*-Phenylenediamine hydrochloride (6 g.) dissolved in 50 c.c. of 50% sulphuric acid is mixed with 4 g. of sodium azide. The solution is then diazotised, with the usual precautions (about 6 g. of sodium nitrite are required), and a further amount of 4 g. of sodium azide added. After keeping the solution for an hour, the bistriazo-compound is extracted with ether and purified by distilling twice in steam. It is obtained as faintly yellow needles, m. p. 5° (Forster and Fierz, *loc. cit.*, p. 1953).

Preparation of Tristriazomesitylene.—A solution of 2 g. of triaminomesitylene hydrochloride in the least amount of water is mixed with 10 c.c. of concentrated hydrochloric acid and 1·5 g. of sodium azide. After cooling to − 15°, the hydrochloride is diazotised by adding 3·2 g. of sodium nitrite (an excess). A further amount of 1·5 g. of sodium azide is added. The crystalline product which separates after the solution has been kept for several hours is filtered off and purified by two distillations in steam. The pure tristriazo-compound is obtained from the distillate as soft white needles, m. p. 50° after crystallisation from light petroleum (Morgan and Davies, *J.*, 1923, **123**, 237).

The preparation of fluoro-derivatives of the aromatic hydrocarbons can be effected by warming the diazonium salt with an excess of aqueous hydrofluoric acid (Griess, *Ber.*, 1885, **18**, 961; Valentiner and Schwarz, D.R.-P. 96,153; Swarts, *Bull. Acad. roy. Belg.*, 1907, 941; Ekbom and Mauzelius, *Ber.*, 1889, **22**, 1846). An alternative method consists in heating a suitable diazoamino-compound with concentrated hydrofluoric acid (Wallach, *Annalen*, 1886, **235**, 255; Wallach and Heusler, *ibid.*, 1888, **243**, 219).

More recently, Balz and Schiemann (*Ber.*, 1927, **60**, **1186**) have found that the replacement of the diazo-group by fluorine takes place smoothly by warming the diazonium fluoroborate. The process is illustrated by the following description.

Preparation of Fluorobenzene.—Benzenediazonium fluoroborate is prepared by adding an excess (60 c.c.) of a 40% solution of fluoroboric acid to a clear diazo-solution prepared from 20 g. of aniline and 40 c.c. of hydrochloric acid, by the addition of sodium nitrite.

The diazonium fluoroborate separates out to form a paste which is filtered. The precipitate is washed with a little fluoroboric acid and then with alcohol and ether—yield 27 g.

The dry diazonium fluoroborate is distilled in quantities of 10 g. Fluorobenzene distils over and is collected in a well-cooled receiver having a side arm to which are attached traps containing aqueous alkali to retain the boron trifluoride which is liberated in the decomposition. The yield of fluorobenzene is nearly quantitative.

The replacement of the diazonium group by Cl or Br is effected most conveniently either by Sandmeyer's method (*Ber.*, 1884, **17**, 1633, 2650) or by Gattermann's method (*ibid.*, 1890, **23**, 1218). The process due to Gattermann, which has been applied to the replacement of the diazo-group by –Br, –Cl, –CNO, –CN, and other groupings, consists in adding copper bronze or copper powder to a solution of the appropriate diazonium salt. It is illustrated below. In Sandmeyer's method the replacement by Br or Cl is effected by adding a solution of cuprous bromine or chloride in the corresponding acid to the diazonium salt and then warming. By a similar process, using cuprous cyanide in potassium cyanide solution or cuprous thiocyanide in potassium thiocyanate solution, the diazonium group can be replaced by –CN or –CNS.

Preparation of Chlorobenzene (1).—A solution of aniline (30 g.) in 67 g. of concentrated hydrochloric acid diluted with 200 c.c. of water is cooled to 0° and diazotised by the addition of a solution of 23 g. of sodium nitrite in 60 c.c. of water. The diazonium solution is then run into 150 g. of a boiling 10% solution of cuprous chloride in hydrochloric acid. Chlorobenzene distils over, the last amounts being driven over by distillation in steam. The chlorobenzene is separated from the distillate, washed with dilute sodium hydroxide, dried, and distilled, b. p. 130°—yield 26 g.

By the same procedure, *m*-chlorobenzoic acid, *m*-nitrochlorobenzene, *o*- and *p*-chlorotoluene, and *o*-chlorophenol have been prepared. The products which are not readily volatile in steam can be taken up in ether and purified by suitable means (Sandmeyer, *Ber.*, 1884, **17**, 1633, 2650).

(2) A solution of benzenediazonium chloride in an excess of hydrochloric acid is prepared from 31 g. of aniline in 150 c.c. of water and 300 g. of hydrochloric acid and 23 g. of sodium nitrite. The solution is stirred with a turbine and 40 g. of moist copper powder are added. When the reaction is complete, the chlorobenzene is isolated by steam distillation—yield 24 g.

By the same process *o*- and *p*-chlorotoluenes are obtained in good yield (60—65%), while *p*-chloronitrobenzene is obtained in 70% yield (Gattermann, *Ber.*, 1890, **23**, 1218).

Preparation of o-*Chlorotoluene*.—The cuprous chloride required for this preparation is obtained by reducing a solution of 125 g. of crystallised copper sulphate and 32·5 g. of sodium chloride in 400 c.c. of hot water by the rapid addition of a solution of 26·5 g. of sodium bisulphite and 17·5 g. of sodium hydroxide in 200 c.c. of water. The mixture is stirred mechanically during the reduction, and when it is complete the mixture is cooled and the precipitate of cuprous chloride allowed to settle. It is then washed by decantation and dissolved in 200 c.c. of concentrated hydrochloric acid.

The diazonium solution is prepared by adding an ice-cold solution of 28 g. of sodium nitrite (28 g.) in 80 c.c. of water to a mechanically stirred mixture of *o*-toluidine (43 g.), 200 c.c. of concentrated hydrochloric acid, and 100 g. of ice cooled by an external bath of ice. The diazonium solution is added to the cuprous chloride solution, which is cooled to 0° and stirred. The mixture, which becomes very thick owing to the formation of an addition compound of the diazo-compound with cuprous chloride, is gradually allowed to warm up to room temperature. The decomposition is finally completed by warming to 60° in a water-bath. *o*-Chlorotoluene is driven over by steam distillation. It is separated from the distillate, washed with a small volume of concentrated sulphuric acid, then with water, and dried in contact with calcium chloride. Pure *o*-chlorotoluene is collected at 155—158°—yield about 75%. *p*-Chlorotoluene is prepared similarly from *p*-toluidine (Marvel and McElvain, *Organic Syntheses*, 1923, **3**, 33).

Preparation of o-*Nitrochlorobenzene*.—*o*-Nitraniline (30 g.), dissolved in 150 c.c. of concentrated hydrochloric acid, is poured over 200 g. of ice. The temperature falls to − 8° to − 10°, and while the mixture is stirred, a solution of 15 g. of sodium nitrite in 50 c.c. of water is added. When a clear solution results, it is poured on 15 g. of copper bronze moistened with hydrochloric acid. A vigorous evolution of gas occurs. When the reaction is over, the mixture is distilled in steam. The *o*-nitrochlorobenzene in the distillate is taken up in ether, washed with dilute aqueous alkali, then with dilute hydrochloric acid, dried, and distilled, b. p. 242° (corr.) m. p. 32°—yield 22 g. (Ullmann, *Ber.*, 1896, **29**, 1878).

Preparation of m-*Nitrochlorobenzene*.—*m*-Nitraniline (55 g.) dissolved in a mixture of 100 c.c. of hot water and 50 c.c. of hydrochloric acid is mixed with 110 c.c. of concentrated hydrochloric acid and rapidly cooled by an external bath of ice and salt, while it is stirred by an efficient mechanically driven stirrer. Diazotisation is effected at 0° or below, by adding a 30% solution of sodium nitrite to the stirred acid solution till there is a faint positive test for nitrous acid. The solution is then filtered and added to a solution of cuprous chloride (prepared from 120 g. of $CuSO_4,5H_2O$, with NaCl and $NaHSO_3$) (compare above) in 150 c.c. of concentrated hydrochloric acid. The temperature of the solution must be between 25° and 30° during this operation. When all the diazonium solution has been added, the mixture is heated under reflux till the evolution of nitrogen ceases. *m*-Nitrochlorobenzene is isolated by steam distilling and subsequently filtering the distillate. The solid product is purified by shaking with 100 c.c. of 1% sodium hydroxide at 50°, and then, after filtering the cooled mixture, washing the solid on the filter funnel with water. After drying, it distils at 124—125°/18 mm., m. p. 44—45°—yield 40—45 g. (Hartman and Brethen, *Organic Syntheses*, 1923, **3**, 79).

Preparation of Bromobenzene.—Aniline (31 g.) in 130 g. of concentrated sulphuric acid, diluted with twice its weight of crushed ice, is diazotised by the addition of an aqueous solution of 23 g. of sodium nitrite. Potassium bromide (130 g.) is added when the diazotisation is complete and then 40 g. of copper powder gradually. After keeping for a short time, the bromobenzene is driven over by a current of steam—yield 22 g., b. p. 155° (Gattermann, *Ber.*, 1890, **23**, 1218).

Preparation of o-*Bromotoluene.*—A solution of 32 g. of *o*-toluidine in 180 c.c. of 40% hydrobromic acid is cooled to 10° and diazotised by the gradual addition of 23 g. of powdered sodium nitrite. After each addition of nitrite, the flask is stoppered and shaken till no more red fumes are present. The temperature must be below 10° throughout the operation. When the diazotisation is complete, 1 g. of copper bronze is added, a reflux condenser attached to the flask, which is heated cautiously till the first signs of decomposition are apparent. The reaction mixture is then cooled by ice while the evolution of nitrogen proceeds vigorously. When the reaction subsides, the mixture is heated on a water-bath for about ½ hour, 200 c.c. of water are added and the mixture is steam distilled. The distillate, which should be about 300 c.c., is made alkaline by adding about 2 g. of powdered sodium hydroxide. The crude *o*-bromotoluene is then separated, shaken with a little concentrated sulphuric acid, then with water, dried with calcium chloride, and rectified, b. p. 178—181°—yield about 22—24 g. (Bigelow, *Organic Syntheses*, 1929, **9**, 22).

Preparation of p-*Bromotoluene.*—A solution of 53 g. of *p*-toluidine and 98 g. of concentrated sulphuric acid in 500 c.c. of water is cooled by an external bath of ice, and when the temperature of the mixture is between 0° and 10°, a solution of 35 g. of sodium nitrite in 63 c.c. of water is added. The temperature must be kept below 10° during the diazotisation. The diazonium solution is added from a dropping funnel to a solution of cuprous bromide heated by a current of steam. *p*-Bromotoluene passes over, and is separated from the distillate by ether. The ethereal solution is then washed with dilute sodium hydroxide and water. The solvent is evaporated, the residue shaken with a small volume of concentrated sulphuric acid, and the bromotoluene finally washed with water and dried with calcium chloride, b. p. 183—185°—yield 60—63 g.

The cuprous bromide is prepared by refluxing a mixture of 32 g. of crystalline copper sulphate, 10 g. of copper turnings, 77 g. of sodium bromide, and 15 g. of sulphuric acid in 500 c.c. of water till the solution becomes brown (Bigelow, *Organic Syntheses*, 1925, **5**, 21).

Preparation of o-*Tolunitrile.*—*o*-Toluidine (43 g.) is mixed with 100 c.c. of concentrated hydrochloric acid and 400 g. of ice and treated at 0° with a 30% solution of sodium nitrite till there is a faint excess of nitrous acid present. The temperature must be kept at 0° by an external bath of ice, and local rises in temperature are avoided by mechanically stirring the mixture. The diazonium solution is neutralised by adding dry sodium carbonate (about 20 g.). It is then added slowly to a solution of cuprous cyanide, which is covered by a layer of benzene and stirred by an efficient rapidly rotating stirrer. The temperature of the mixture should be between 0° and 5° throughout the operation, and when all the diazonium solution has been added, is slowly allowed to rise to that of the room. After keeping for some hours, it is gradually warmed to 50° by immersion in a warm water-bath and then cooled. The benzene layer is separated and distilled in steam. The benzene solution from the distillate is dried with calcium chloride and fractionated, first at atmospheric pressure to remove the solvent, and then under reduced pressure. *o*-Tolunitrile is collected at 94—96°/20 mm.—yield about 30 g.

p-Tolunitrile is obtained in the same way from *p*-toluidine.

The solution of cuprous cyanide required for this preparation is obtained by stirring cuprous chloride (prepared from 125 g. of $CuSO_4,5H_2O$ according to the directions given above) with 200 c.c. of water, and then adding a solution of 65 g. of sodium cyanide in 100 c.c. of water (Clarke and R. R. Read, *Organic Syntheses*, 1925, **4**, 69).

Preparation of Phenylthiocyanate.—A solution of 31 g. of aniline in 100 g. of concentrated sulphuric acid diluted with 200 c.c. of water, is cooled to 0° and diazotised by the addition of 23 g. of sodium nitrite dissolved in water. The diazonium solution is stirred and mixed with an ice-cold solution of potassium thiocyanate and a paste of cuprous thiocyanate, which has been prepared by adding 35 g. of potassium thiocyanate to a solution of 80 g. of copper sulphate containing 150 g. of ferrous sulphate. The evolution of nitrogen is complete after about 3 hours, when the phenylthiocyanate is steam distilled. It is separated from the distillate with ether, dried in contact with anhydrous magnesium sulphate, and fractionated, b. p. 232° (Gattermann and Hausskneecht, *Ber.*, 1890, **23**, 738).

Preparation of Phenylcarbimide.—Aniline (10 g.) dissolved in 20 g. of concentrated sulphuric acid diluted with 100 c.c. of water is diazotised with 7·5 g. of sodium nitrite. Potassium cyanate (9 g.) is added to the diazonium solution and then 5 g. of copper powder. An evolution of nitrogen commences. Later a further amount of 5 g. of copper powder is added. The phenylcarbimide, which rises to the surface during the preparation, is skimmed off with a spoon and freed from inorganic matter by solution in chloroform.

Further amounts of phenylcarbimide are obtained by adding more copper powder till there is no further evolution of nitrogen. The combined chloroform solutions are dried and fractionated, yield about 2·5 g., b. p. 163—167° (Gattermann, *Ber.*, 1890, **23**, 1225; Gattermann and Cantzler, *ibid.*, 1892, **25**, 1086).

4. *Replacement by Other Groups.*—(a) *Aryl.* It is frequently observed that the replacement reactions discussed in the previous section yield smaller or greater amounts of derivatives of diphenyl (compare Griess, *Ber.*, 1885, **18**, 965; Hirsch, *ibid.*, 1890, **23**, 3705; 1892, **25**, 1973). This is particularly noticeable with nitrobenzenediazonium salts. Thus diazotised *o*-nitraniline furnishes only a poor yield of *o*-chloronitrobenzene when treated with cuprous chloride under the conditions of the Sandmeyer reaction; the principal product being 2 : 2′-dinitrodiphenyl. The diazonium chlorides derived from *m*-nitraniline, 5-chloro-2-nitraniline, 3-nitro-*p*-toluidine, 2-nitro-*p*-toluidine, 6-nitro-*o*-toluidine, 5-nitro-*o*-toluidine, and 4-nitro-*o*-toluidine behave similarly, the replacement of the diazonium group by halogen being the minor reaction (Ullmann and Forgan, *Ber.*, 1901, **34**, 3802; Ullmann and Frentzel, *ibid.*, 1905, **38**, 725; v. Niementowski, *ibid.*, 1901, **34**, 3325). Apparently the experimental conditions are an important factor in determining the yield of the diphenyl derivative. By careful control using the Sandmeyer reaction it is possible to obtain an excellent yield of *m*-nitrochlorobenzene from *m*-nitraniline (see p. 343).

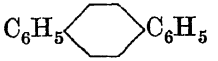
Some diazonium solutions which behave normally under the conditions of the Sandmeyer reaction can be made to furnish diphenyl derivatives by treatment with alcohol and either zinc dust, copper powder, or iron powder (Gattermann and Ehrhardt, *Ber.*, 1890, **23**, 1226). Under these conditions an aqueous acid solution of benzenediazonium sulphate yields diphenyl; diazotised β-naphthylamine furnishes ββ′-dinaphthyl (Chattaway, *J.*, 1895, **67**, 653).

Preparation of Diphenyl.—An aqueous acid solution of benzenediazonium sulphate is prepared by treating a solution of 31 g. of aniline in 40 g. of concentrated sulphuric acid and 150 c.c. of water with 23 g. of sodium nitrite in water. The solution is mixed with 100 g. of 90% alcohol and 50 g. of copper powder are added slowly while the mixture is stirred. After 1 hour the diphenyl is driven over by steam, m. p. 70°—yield 6—7 g.

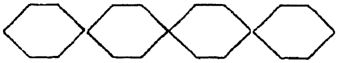
The copper powder may be replaced by zinc dust (100 g.).

The temperature of the reaction must be kept below 30—40°.

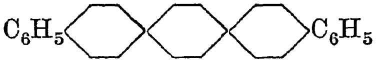
In this preparation of diphenyl an appreciable amount of material which is not volatile in steam is formed. This consists largely of diphenylbenzene (I), didiphenyl (II), and didiphenylbenzene (III) (Gerngross, Schachnow, and Jonas, *Ber.*, 1924, **57**, 747). The yield of the higher hydrocarbons is increased by carrying out the reaction in acetic acid containing some formic acid.



(I.)



(II.)



(III.)

Preparation of Diphenylbenzene, Didiphenyl, and Didiphenylbenzene.—Aniline (85 g.) dissolved in a hot solution of 170 g. of concentrated sulphuric acid and 520 g. of acetic acid is rapidly cooled to 5—10° and diazotised by the addition of 110 g. of amyl nitrite. When the diazotisation is complete, 50 g. of formic acid are added, the solution is cooled to 0—2° and stirred vigorously by a mechanically driven stirrer. Copper powder (10 g.) is then added, and a further 40 g. over a period of 3 hours. The reaction is complete when the solution no longer couples with R salt (4 hrs.).

Diphenyl is isolated from the product by distillation in steam. The distillate is made alkaline with sodium carbonate, extracted with ether, and the ethereal solution washed with 10% sulphuric acid, with 2*N*-sodium hydroxide, dried, and fractionated to separate the diphenyl from the amyl acetate which is formed in the reaction. The diphenyl is obtained pure by crystallisation from alcohol—yield 7 g.

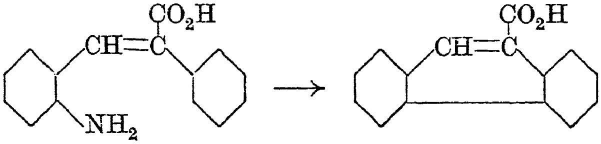
The non-volatile residue in the flask is an ochre-yellow flocculent precipitate, and a further amount is obtained by neutralisation with sodium carbonate. It is collected on a filter and washed with water, and then dried at 120° and stirred till it can be powdered at room temperature. It consists of copper powder mixed with the higher hydrocarbons. The separation is effected by sublimation from a copper flask the neck of which is inserted into the neck of a distillation flask and luted. The sublimation is continued at 30 mm. till the heating bath of graphite has reached a temperature of 400°. The sublimate, 17 g., is extracted with 150 c.c. of benzene in a Soxhlet apparatus. An insoluble residue of crude didiphenylbenzene remains (2·5 g.), which is purified by boiling with 100 times its weight of xylene followed by crystallisation from quinoline—m. p. 388° (corr.).

The benzene extract deposits crude didiphenyl on cooling (3·2 g.), while evaporation of the filtrate to half its volume furnishes a mixture of diphenylbenzene and didiphenyl. Evaporation of the solution to dryness yields crude diphenylbenzene.

The crude diphenylbenzene yields the pure product on distillation under reduced pressure, b. p. 214—250°/15 mm., and a further amount is obtained by treating the other fractions similarly—yield 5·4 g., m. p. 205°.

The residue from the separation of the diphenylbenzene is sublimed under a high vacuum. Pure didiphenyl is collected between 180° and 230°—yield 1·6 g., m. p. 302°; didiphenylbenzene at 285—290° (Gerngross and Dunkel, *Ber.*, 1924, **57**, 742).

An interesting application of the diphenyl preparation by the diazo-reaction is the synthesis of phenanthrene and its derivatives. When the diazonium salt from α-phenyl-*o*-aminocinnamic acid is treated in aqueous solution with copper powder, the diazonium group is eliminated, and the two phenyl groups unite to give phenanthrene carboxylic acid (Pschorr, *Ber.*, 1896, **29**, 496). This reaction has been extended by Pschorr to the synthesis of other substituted derivatives of phenanthrene (*Ber.*, 1906, **39**, 3106).



A similar type of internal condensation occurs when solutions of diazonium salts from some substituted *o*-aminobenzophenones are heated. Fluorenones are formed with *o*-hydroxy-substituted benzophenones as by-products (Ullmann and Mallet, *Ber.*, 1898, **31**, 1694).

*Preparation of Phenanthrene-*9*-carboxylic Acid.*—Dilute sulphuric acid (*d*, 1·19) is added to a suspension of α-phenyl-*o*-aminocinnamic acid (12 g.) in 160 c.c. of water. The resulting solution is diazotised by the addition of 4 g. of sodium nitrite in 20 c.c. of water. After filtering, the solution is shaken with 14 g. of copper powder till the diazonium salt has completely decomposed, as shown by its failure to couple with α-naphthylamine. The end of the reaction can also be recognised by the green colour of the solution. The suspended matter, consisting of copper powder and phenanthrene carboxylic acid, is collected and extracted with dilute aqueous ammonia. The acid is precipitated from the ammoniacal solution by adding an excess of dilute acid, m. p. 250°—yield 93%.

Another method for the preparation of diphenyl and its substituted derivatives consists in allowing the diazo-anhydride to react with an aromatic hydrocarbon (Kühling, *Ber.*, 1895, **28**, 41; Bamberger, *ibid.*, p. 403). Thus sodium *p*-nitrobenzenediazotate mixed with benzene and sufficient acetic acid to liberate the diazo-anhydride furnishes *p*-nitrodiphenyl in good yield.

$$NO_2{\cdot}C_6H_4{\cdot}N_2OH + C_6H_5 \longrightarrow NO_2{\cdot}C_6H_4{\cdot}C_6H_5 + N_2 + H_2O$$

More recently, this process has been modified and applied to the preparation of a large number of substituted derivatives of diphenyl. It is accompanied, however, by other reactions, such as replacement of the diazo-group by hydrogen and by the formation of azo-compounds (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339; Gomberg and Pernert, *ibid.*, 1926, **48**, 1372). The experimental procedure is best indicated by the following.

Preparation of p-*Bromodiphenyl.*—*p*-Bromaniline (43 g.) is melted with 20 c.c. of water and then 50 c.c. of concentrated hydrochloric acid are added to the stirred mixture. It is heated till a practically clear solution is obtained, and then rapidly cooled while stirred so as to obtain the hydrochloride in as fine a state of division as possible. The ice-cold suspension is diazotised by the addition of sodium nitrite (about 18 g.) in twice its weight of water till there is a faint yet definite indication for free nitrous acid in the solution.

The diazotised solution is then poured into a $1\frac{1}{2}$-l. wide-necked bottle surrounded by ice. Benzene (300 c.c.) is now added, and the mixture stirred with an efficient mechanically driven stirrer while 58 c.c. of 5*N*-sodium hydroxide are added drop by drop from a dropping funnel. The addition of the alkali must be so regulated that the yellow precipitate which is produced can react readily with the benzene. The temperature of the mixture should be about 5°, and it is allowed to warm up to room temperature after all the alkali has been added. The benzene layer is separated and steam distilled. After all the benzene has been driven over, the receiver is changed and the distillation flask heated in an oil-bath at 170°. *p*-Bromodiphenyl passes over with the steam. It is collected by filtering the distillate and purified by dissolving in about 200 c.c. of hot ethyl alcohol, and then adding 5 g. of zinc dust and about 5 c.c. of concentrated hydrochloric acid. Pure *p*-bromodiphenyl crystallises from the hot filtered solution, m. p. 90°—yield 20—21 g. (Gomberg and Bachmann, *Organic Syntheses*, 1928, **8**, 43).

Similarly diphenyl has been prepared by the reaction of sodium benzenediazotate with benzene. The yield is, however, only 11%. The benzene in this reaction can be replaced by thiophene, which yields phenylthiophene; nitrobenzene furnishes 4-nitrodiphenyl. Bromobenzene and benzonitrile react similarly. The diazo-compound may be derived from chlor- or brom-anilines, the toluidines, nitranilines, *m*- or *p*-aminobenzonitrile or *p*-aminodiphenyl. Unfortunately, the yields from most of these preparations are low, usually between 10 and 40% of the theoretical. A discussion of the nature of this reaction is contained in a paper by Grieve and Hey (*J.*, 1934, 1797).

An alternative method consists in adding the dry diazonium chloride to the appropriate hydrocarbon such as benzene, or naphthalene mixed with some anhydrous aluminium chloride (Möhler and Berger, *Ber.*, 1893, **26**, 1196, 1994). Thus with benzene, diphenyl is formed, while naphthalene yields a mixture of α- and β-phenylnaphthalenes. The method has also been used for the preparation of phenylpyridine and phenylquinoline, and in these cases the addition of aluminium chloride is unnecessary.

$$\mathrm{Ph{\cdot}N_2Cl + C_6H_6 \longrightarrow Ph{\cdot}C_6H_5 + N_2 + HCl}$$

(b) *Nitro-Group.*—This replacement can be effected by treatment of a solution of a suitable diazonium nitrate with cuprous oxide and nitrous acid (Sandmeyer, *Ber.*, 1887, **20**, 1494). Another procedure for this reaction is to add copper powder to an aqueous solution or suspension of the double compound of mercuric nitrite and the diazonium nitrate (Hantzsch and Blagden, *Ber.*, 1900, **33**, 2551), or to treat the diazonium salt with an excess of potassium nitrite and a suspension of cupro cupric sulphite.

Preparation of β-Nitronaphthalene from β-Naphthylamine.—β-Naphthylamine (7 g.) is added to a boiling solution of 15 g. of nitric acid (*d*, 1·4) and 250 c.c. of water, the solution rapidly cooled and the paste of β-naphthylamine nitrate diazotised by adding 12 g. of sodium nitrite in 40 c.c. of water. The solution is then added to a suspension of cuprous oxide in water (prepared from 50 g. of $CuSO_4,5H_2O$ by reduction with glucose and aqueous alkali, the alkali being subsequently neutralised by acetic acid) slowly and with cooling. About 20 minutes after mixing, sufficient alcohol is added to dissolve the foam. The mixture is kept for several hours and then steam distilled. The solid which is obtained in the distillate is a mixture of naphthalene and nitronaphthalene. It is collected and heated in a small dish on a water-bath for 2 hours to sublime away most of the naphthalene. The residue, crystallised from alcohol, is pure β-nitronaphthalene, m. p. 78—79°—yield 0·5 g. (Sandmeyer, *Ber.*, 1887, **20**, 1497).

Preparation of Nitrobenzene from Aniline.—A diazonium solution prepared from 9 g. of aniline, 50 c.c. of water, 20 g. of concentrated nitric acid, and 15 g. of sodium nitrite is added to a suspension of cuprous oxide. After keeping for 1 hour, the nitrobenzene is driven over in steam, taken up from the distillate with ether, and freed from phenol and nitrophenol by washing with alkali. After drying and fractionating, 4 g. of nitrobenzene are obtained (Sandmeyer, *loc. cit.*).

Preparation of p-*Dinitrobenzene.*—*p*-Nitraniline (28 g.) in 100 c.c. of nitric acid (*d*, 1·4) is diazotised by the addition, at 0°, of a concentrated aqueous solution of 75 g. of sodium nitrite and then added gradually to a suspension of cuprous oxide (from 200 g. of $CuSO_4,5H_2O$). Alcohol is added at intervals to moderate the foaming. The mixture is kept for 2 days and then steam distilled. *p*-Dinitrobenzene slowly collects in the distillate, from which it is separated by filtration. A further amount is obtained by extracting the aqueous portion of the distillate with ether. *p*-Dinitrobenzene crystallises from alcohol, m. p. 172—173°—yield 8 g. (Meisenheimer and Patzig, *Ber.*, 1906, **39**, 2528).

(c) *Sulphinic Group.*—The general procedure consists in saturating a solution of the diazonium sulphate in dilute sulphuric acid with sulphur dioxide and then adding copper powder. This method has been successfully applied to the preparation of benzenesulphinic acid and many of its homologues and halogen and alkoxy-substituted derivatives. Apparently only poor yields of the required sulphinic acid are obtained from *m*-toluidine (Gattermann, *Ber.*, 1899, **32**, 1136; Troeger and Hille, *J. pr. Chem.*, 1903, [ii], **68**, 297; 1905, [ii], **71**, 207). An elegant modification for the isolation of the sulphinic acid has been introduced by J. Thomas. It consists in precipitating the sulphinic acid as its ferric salt from acid solution (*J.*, 1909, **95**, 342).

Preparation of Benzenesulphinic Acid.—A solution of aniline (10 g.) in 150 c.c. of water and 20 g. of concentrated sulphuric acid is diazotised by the addition of a solution of 8 g. of sodium nitrite in 40 c.c. of water. After the diazotisation, an ice-cold mixture of 30 c.c. of water and 40 g. of concentrated sulphuric acid is added, and while the solution is still cooled in ice, sulphur dioxide is passed in till there is no further increase in weight. The solution should not develop any serious colour during this operation and should be quite clear. When it is saturated with sulphur dioxide, it is stirred and copper powder added gradually till no more nitrogen is evolved. When the reaction is complete, the suspended copper is filtered off and washed with several small amounts of very dilute ammonia to remove any sulphinic acid which may have separated.

The ammoniacal washings are added to the sulphuric acid filtrate. The combined filtrate and washings should be acid. It is then treated with a very concentrated aqueous solution of ferric chloride as long as any precipitate is formed. The precipitate, which is the ferric salt of benzenesulphinic acid, is filtered off, washed with water, and dried with the aid of a little alcohol—yield 16 g.

The ferric salt is decomposed by aqueous alkali with the formation of ferric hydroxide and a solution of the sodium salt of the sulphinic acid. On acidifying, the sulphinic acid is liberated, and may be isolated by extraction with ether (Gattermann, *loc. cit.*; Thomas, *loc. cit.*).

(d) *Preparation of Aryl-arsinic* and -stibinic Acids.*—The replacement of the diazonium group by $-AsO_3H_2$ is generally effected by the action of sodium arsenite in alkaline solution (Bart, *Annalen*, 1922, **429**, 55).

Preparation of p-*Tolylarsinic Acid.*—A suspension of *p*-toluidine (10·7 g.) in 100 c.c. of water is mixed with 35 c.c. of hydrochloric acid (*d*, 1·126), the resulting solution cooled to 5° and diazotised by the addition of 100 c.c. of *N*-sodium nitrite solution. When the diazotisation is complete, a solution of 20 g. of sodium arsenite (Na_2HAsO_3) in 100 c.c. of water is added, and while the mixture is being stirred, 125 c.c. of *N*-sodium hydroxide are added gradually. The solution is stirred till it gives no further test for a diazo-compound (3—4 hours). The temperature of the solution during the preparation can rise to 15° without any serious effect on the yield.

The solution is evaporated on the water-bath to about 200 c.c. and filtered from small amounts of tarry matter. The filtrate is rendered feebly acid by adding about 7 c.c. of concentrated hydrochloric acid and then boiled with decolorising charcoal and filtered hot. The addition of 8 c.c. of concentrated hydrochloric acid to the hot filtrate causes the separation of *p*-tolylarsinic acid as a paste of crystals—yield 12 g. The product is practically pure. It may be further purified by trituration with cold ethyl acetate, followed by recrystallisation from water (Bart, *loc. cit.*, p. 82).

Preparation of p-*Nitrophenylarsinic Acid.*—*p*-Nitraniline (13·8 g.) is dissolved in 80 c.c. of hot hydrochloric acid (*d*, 1·126), the solution cooled and then diazotised by the addition of 8 g. of sodium nitrite in 25 c.c. of water, the temperature being kept below 15°. When the diazotisation is complete, the solution is diluted to 1000 c.c., and treated at about 10° with 5*N*-sodium hydroxide till the acid reaction to congo paper has just disappeared. The solution is then poured in a thin stream into 400 c.c. of 10% sodium arsenite diluted with 450 c.c. of water. When the evolution of nitrogen ceases, the solution is evaporated to 400 c.c., acidified feebly with hydrochloric acid and filtered. The filtrate is then rendered acid to congo paper and evaporated till crystals commence to separate—yield about 11 g. The product is purified by crystallisation from water using decolorising charcoal. It forms colourless needles, m. p. above 300° dec. (Bart, *loc. cit.*, p. 95).

(e) *Thiol, Sulphide and Disulphide.*—A general method for the preparation of thiophenols by the diazo-reaction is due to Leuckart (*J. pr. Chem.*, 1890, [ii], **41**, 179). It consists in mixing ice-cold solutions of a diazonium chloride and potassium xanthogenate in molecular proportions. The aryl derivative of ethyl thiocarbonic acid separates on warming, and this on hydrolysis with alcoholic potash yields a thiophenol.

$$Ph{\cdot}N_2Cl + EtO{\cdot}CS{\cdot}SK \longrightarrow N_2 + KCl + Ph{\cdot}S{\cdot}CS{\cdot}OEt \xrightarrow[KOH]{} PhSH$$

The formation of sulphides and disulphides occurs on adding an alkali sulphide to a diazonium solution; less rarely, the product contains a thiophenol as well (Graebe and Mann, *Ber.*, 1882, **15**, 1683; Purgotti, *Gazzetta*, 1890, **20**, 24). This reaction is very satisfactory for the preparation of the disulphide from the diazo-compounds derived from anthranilic acid.

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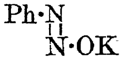
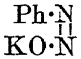
* Recently the suffix *arsinic acid* has been changed to *arsonic* acid by the Chemical Society.

5. *Action of Alkalies* : *Formation of Diazotates.*—The addition of a solution of benzenediazonium chloride to excess of a cold concentrated aqueous solution of potassium hydroxide causes the separation of a potassium salt having the formula $\mathrm{Ph{\cdot}N_2{\cdot}OK}$ (compare Griess, *J.*, 1867, **20**, 46). If the temperature has not been allowed to rise unduly, the freshly prepared salt couples with β-naphthol. If, however, the potassium salt is warmed with an excess of potash, the power to couple with β-naphthol is lost, although the diazonium chloride is still formed on acidifying with hydrochloric acid. There appear therefore to be two isomeric potassium salts of the formula $\mathrm{Ph{\cdot}N_2{\cdot}OK}$, which differ in their behaviour to β-naphthol. They are not derivatives of benzenediazonium hydroxide, for it is possible to isolate from one of them by the action of acetic acid a diazohydroxide, $\mathrm{Ph{\cdot}N_2{\cdot}OH}$, which has acidic properties and is soluble in ether (compare this with the diazonium hydroxide, p. 335). The other potassium salt yields a diazo-anhydride $\mathrm{(Ph{\cdot}N_2)_2O}$. The potassium salts are formulated as $\mathrm{Ph{\cdot}N{:}N{\cdot}OK}$, which allows of the existence of two stereoisomers on the Hantzsch–Werner hypothesis.

(I.)



$$\begin{matrix}\mathrm{Ph{\cdot}N}\\ \|\\ \mathrm{N{\cdot}OK}\end{matrix}$$



$$\begin{matrix}\mathrm{Ph{\cdot}N}\\ \|\\ \mathrm{KO{\cdot}N}\end{matrix}$$

(II.)

The formula (II) has been given to the labile potassium salt which couples with β-naphthol and which is transformed into (I) on warming with alkali. These formulæ not improbably may require to be interchanged in view of the recent work on the steric configuration of the oximes (Meisenheimer, Zimmermann, and v. Kummer, *Annalen*, 1926, **446**, 205; W. H. Mills, *B. A. Report*, 1932, 37). Instead of the terms *syn* and *anti*, which are frequently used to distinguish these stereoisomers, it is proposed to distinguish them by the prefixes *labile* and *stable*. Corresponding with the two series of alkali salts, are two series of cyanides, which are obtained by mixing the diazonium salt with concentrated aqueous alcoholic potassium cyanide at — 10°. These diazo-cyanides are coloured and sparingly soluble in water. They are quite distinct in their properties from the true diazonium cyanides which have been prepared by evaporation of a diazonium hydroxide with hydrogen cyanide, and which resemble the alkali cyanides in being colourless and soluble in water. The *labile* diazo-cyanides couple with β-naphthol, but on keeping they gradually lose this property, the m. p. rising as the change to the *stable* diazo-cyanide proceeds (Hantzsch and Danziger, *Ber.*, 1897, **30**, 2529).

Preparation of Labile Benzene Potassium Diazotate.—A 15% solution of benzenediazonium chloride (10 c.c.) is slowly added to a mixture of 140 g. of potassium hydroxide and 60 c.c. of water cooled to 5°. The temperature is allowed to rise to 15—20°, when the potash dissolves, and the potassium benzene diazotate separates. It is collected by filtration, drained on porous earthenware, and quickly recrystallised by dissolving in 3 c.c. of alcohol at − 5°, filtering, and adding 25—30 c.c. of dry ether. The potassium salt is thus obtained as white silky needles.

If the mixture of diazotate and alkali is warmed to 130°, it loses its power of coupling with β-naphthol and the stable diazotate results. The stable diazotate from *p*-nitrobenzenediazonium chloride is obtained at a lower temperature.

Preparation of Stable p-*Nitrobenzene Sodium Diazotate.*—A 10% solution of *p*-nitrobenzenediazonium chloride, prepared from 54 g. of *p*-nitraniline, is poured rapidly into 1600 c.c. of 18% aqueous sodium hydroxide which is warmed to 50—60° and stirred vigorously. A yellow solution is formed almost immediately, and golden-yellow platelets of the sodium salt commence to separate. The amount increases on cooling, and after several hours, the precipitate is collected—yield 95% of theoretical (Schraube and G. Schmidt, *Ber.*, 1894, **27**, 518).

Preparation of Labile p-*Methoxybenzene Potassium Diazotate.*—A solution of freshly prepared *p*-methoxybenzenediazonium bromide (1 g.) in 2 c.c. of water is added to a solution of 2·65 g. of potassium hydroxide in an equal volume of water cooled to − 10°. The diazotate is precipitated as white leaflets. It is drained and dried on a porous tile in a vacuum desiccator over phosphorus pentoxide. The salt is hygroscopic and becomes tarry in moist air. *ψ*-Cumene potassium diazotate is prepared similarly (Hantzsch, *Ber.*, 1900, **33**, 2158).

Although both series of salts yield a diazonium salt on acidification with mineral acid, they behave differently with acetic acid. The labile salts yield diazoanhydrides, which are highly coloured explosive solids and are hydrolysed by alkali to diazotates. The stable diazotates furnish diazohydrates, $R\cdot N{:}N\cdot OH$, which in general are soluble in such organic solvents as ether, benzene, and chloroform. They are extracted from ethereal solution by alkali with the formation of diazotate. In aqueous solution or in chloroform or benzene they probably isomerise more or less readily to primary nitrosamines (compare Hantzsch, *Ber.*, 1912, **45**, 3036; Hantzsch and Pohl, *ibid.*, 1902, **35**, 2964).

$$R\cdot N{:}N\cdot OH \longrightarrow R\cdot NH\cdot NO$$

Secondary nitrosamines result from the reaction of alkali diazotates with alkyl iodides (Schraube and Schmidt, *loc. cit.*). With acyl halides nitrosoanilides are formed. Thus nitrosobenzanilide results when benzoyl chloride is shaken with an alkaline solution of benzene sodium diazotate. Acetic anhydride reacts with an alkaline solution of *p*-toluene sodium diazotate to give nitrosoacet-*p*-toluidide (v. Pechmann and Frobenius, *Ber.*, 1894, **27**, 651).

$$R\cdot N_2\cdot ONa + Ph\cdot CO\cdot Cl \quad - \quad R\cdot N(NO)\cdot CO\cdot Ph + NaCl$$

$$R\cdot N_2\cdot ONa + CH_3I \quad - \quad R\cdot N(NO)\cdot CH_3 + NaI$$

In connection with the ready conversion of diazotates into nitroso-compounds, it is of interest to note that nitramines are formed by oxidation of diazo-compounds in alkaline solution.

$$Ph\cdot N_2\cdot OK \longrightarrow Ph\cdot NK\cdot NO_2$$

Preparation of Phenylnitramine.—Aniline (10 g.) is diazotised in as concentrated solution as possible containing 2½ mol. proportions of hydrochloric acid. The diazonium solution is poured in a thin stream into a solution of potassium ferricyanide (71 g.), which is cooled in ice and mixed with 120 g. of 20% sodium hydroxide solution. Efficient cooling is necessary during this operation. The solution is kept at 0° till it no longer couples with *R* salt (about 70—80 hours). The solution is then acidified with 30% sulphuric acid while it is still cooled in ice, till it turns congo paper a pure blue colour. It is then extracted several times with ether. The nitramine is extracted from the ethereal solution by shaking it several times with concentrated ammonia. The ammoniacal solutions are combined, boiled with decolorising charcoal, concentrated by evaporation, and then acidified after cooling in ice. The nitramine separates as a paste of crystals, which are washed and dried on porous earthenware, m. p. 46—47° (Bamberger, *Ber.*, 1893, **26**, 472; 1894, **27**, 363).

6. *Reaction of Diazonium Salts with Amines*: (a) *Formation of Diazoamino-Compounds.*—The addition of a diazonium compound to a primary or secondary amine yields a diazoamino-compound as the initial product.

$$Ph{\cdot}N_2{\cdot}Cl + RRNH \longrightarrow Ph{\cdot}N_2{\cdot}NRR + HCl$$

This reaction proceeds quite readily with secondary aliphatic amines, being effected by adding the neutral diazonium salt solution to an aqueous solution of the amine, the temperature being kept at 0°. Primary aliphatic amines, in general—benzylamine is an exception—react to yield bisdiazoamino-compounds of the type $R{\cdot}N(N_2{\cdot}Ph)_2$. In some instances it is possible to regulate the conditions so that the product contains a notable proportion of the monodiazoamino-compound (Goldschmidt and Holm, *Ber.*, 1888, **21**, 1016; Goldschmidt and Badl, *ibid.*, 1889, **22**, 933; Dimroth, *ibid.*, 1905, **38**, 2328; Dimroth, Eble, and Gruhl, *ibid.*, 1907, **40**, 2390).

Both types of condensation take place with the aromatic primary aromatic amines, although the formation of a monodiazoamino-compound is the more common. It is brought about by the reaction of the diazonium salt, in concentrated aqueous solution, with an aqueous solution of the appropriate amine hydrochloride, sodium acetate being added when the reactants have been mixed.

Preparation of Diazoaminobenzene.—A solution of 5 g. of aniline in a mixture of 18 c.c. of concentrated hydrochloric acid and 50 c.c. of water is diazotised. A solution of 6·5 g. of aniline hydrochloride in 30 c.c. of water is added, and then a concentrated solution of 25 g. of crystalline sodium acetate. The diazoamino-compound separates out, and after about ½ hour it is collected, washed with water, and dried on porous earthenware. It crystallises from light petroleum (b. p. 70—100°) as golden-yellow crystals, m. p. 98°.

This general method can be applied to the preparation of other diazoamino-compounds of the benzene series.

The condensation may also be effected by adding the diazonium solution to an alcoholic or acetic acid solution of the amine and subsequently adding sodium acetate.

Under the conditions described above for the preparation of diazoamino compounds, some primary aromatic amines may yield an appreciable amount of the isomeric amino-azo-compound. This occurs particularly with aminonaphthalenes which form aminoazo-compounds almost exclusively. Alkyl arylamines, if the *para*-position is free, tend to yield aminoazo-compounds rather than diazoamino-compounds. *m*-Phenylenediamine also yields amino-azo-compounds. The presence of substituents in the aromatic nucleus has an influence on the ease or completeness with which aminoazo-compounds are formed. A full account of this is given by Morgan and Micklethwait (*J.*, 1907, **91**, 370), who also give references to earlier papers. As a further complication in the preparation of diazoamino-compounds, the product may not have the expected structure. Thus diazotised β-naphthylamine reacts with 4-*m*-xylidine to give *m*-xylene-4-azo-β-naphthylamine (Norman, *J.*, 1919, **115**, 675). This complication is probably due to an interchange of amino- and diazo-groups, a change which has been observed with several pairs of amine hydrochlorides and diazo-salts. Thus diazosulphanilic acid and *p*-toluidine, if mixed in aqueous solution, yield some sulphanilic acid and *p*-toluenediazo-chloride (Griess, *Ber.*, 1882, **15**, 2190).

The formation of bisdiazoamino-compounds from arylamines takes place by the action of a diazonium salt on a monodiazoamino-compound dissolved in alcohol containing sodium alkoxide, or by coupling the primary amine with the diazonium salt in alcoholic solution containing sodium alkoxide.

(b) *Formation of Aminoazo-Compounds.*—It has already been stated that some primary amines, such as the naphthylamines and *m*-phenylenediamine yield aminoazo-compounds directly under conditions which normally lead to the formation of diazoamino-compounds from less reactive amines. Aminoazo-compounds can be prepared from the diazoamino-compound by keeping it in an excess of the amine containing some dissolved amine hydrochloride.

$$\mathrm{PhNH{\cdot}N{:}N{\cdot}Ph \longrightarrow PhN{:}N{\cdot}C_6H_4{\cdot}NH_2}.$$

It seems not improbable that this apparent rearrangement is due to the fission of the diazoamino-compound into its generators, followed by reaction of the resulting diazo-compound with the nucleus of the amine. Evidence in support of this view has been summarised by K. H. Meyer (*Ber.*, 1921, **54**, 2267), who has also shown that the formation of aminoazo-compounds from aniline can be accomplished without the intermediate formation of diazoamino-compounds if suitable experimental conditions are chosen.

7. *Reaction of Diazonium Salts with Phenols.*—The formation of hydroxyazo-compounds by the reaction of diazonium salts with phenols has been discussed already on p. 96.

8. *Reduction of Diazo-Compounds. Formation of Aryl Hydrazines.*—The reduction of a diazonium salt by tin and hydrochloric acid results in the formation of an arylhydrazine (V. Meyer and Lecco, *Ber.*, 1883, **16**, 2976; E. Fischer, *ibid.*, 1884, **17**, 572, *footnote*). This

reaction has been used, not only for the preparation of phenylhydrazine, but also to prepare the naphthylhydrazines and many of the nuclear-substituted derivatives of phenylhydrazine (Neufeld, *Annalen*, 1888, **248**, 93). It has even been applied to the reduction of diazotised *o*- and *m*-nitranilines for the preparation of the corresponding nitrophenylhydrazines (Bischler, *Ber.*, 1889, **22**, 2801).

A more convenient and general method of preparing arylhydrazines consists in reducing the appropriate diazosulphonate with bisulphite or sulphur dioxide, and subsequently hydrolysing the hydrazinesulphonic acid thus formed (E. Fischer, *Annalen*, 1877, **190**, 71).

$$PhN_2Cl + Na_2SO_3 \longrightarrow PhN{:}N{\cdot}SO_3Na + NaCl$$

$$PhN{:}N{\cdot}SO_3Na + NaHSO_3 + H_2O \longrightarrow Ph{\cdot}NH{\cdot}NHSO_3Na + NaHSO_4$$

$$PhNH{\cdot}NHSO_3Na + HCl + H_2O \longrightarrow Ph{\cdot}NH{\cdot}NH_2,HCl + NaHSO_4$$

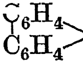
Preparation of Phenylhydrazine (*Method* 1).—A solution of aniline (10 g.) in 200 c.c. of concentrated hydrochloric acid is diazotised by the addition of 8 g. of sodium nitrite in 50 c.c. of water with the usual precautions. An ice-cold solution of 50 g. of stannous chloride in 45 c.c. of concentrated hydrochloric acid is added to the ice-cold diazo-solution. A precipitate of phenylhydrazine hydrochloride separates. It is collected after keeping for about ½ hour. After thoroughly draining, the free base is liberated by the addition of an excess of sodium hydroxide solution. The phenylhydrazine is taken up in ether, the ethereal solution dried, and after removing the solvent the product is distilled under reduced pressure, b. p. 120°/12 mm. (Meyer and Lecco, *loc. cit.*).

(*Method* 2.)—A solution of 28 g. of aniline in diluted hydrochloric acid (80 c.c. of acid and 100 c.c. of water) is diazotised and the resulting solution added to a suspension of 160 g. of sodium sulphite (crystals) and 24 g. of anhydrous sodium carbonate in about 100 c.c. of water. The mixture must be stirred during the addition of the diazo-solution. The diazosulphonate is precipitated as an orange-coloured voluminous solid. When the formation of the sulphonate is complete, the mixture is warmed to 30° and saturated with sulphur dioxide. The solution is then warmed to about 70° and filtered. The addition of concentrated hydrochloric acid (200 c.c.) to the filtrate causes the separation of phenylhydrazine hydrochloride, which is collected after keeping overnight (E. Fischer, *Annalen*, 1877, **190**, 71; Cohen, *Practical Organic Chemistry*, 1924, p. 196).

Preparation of p-*Nitrophenylhydrazine*.—A solution of *p*-nitrobenzenediazonium chloride, from 10 g. of *p*-nitraniline and 21 g. of concentrated hydrochloric acid, is filtered and added slowly to an ice-cold solution of 41 g. of sodium sulphite crystals in 100 c.c. of water containing 4 g. of sodium hydroxide. The solution is stirred mechanically during the addition, which should require about 5 minutes. After keeping for a further period of 5 minutes, the solution is acidified with concentrated hydrochloric acid (70 c.c.) and then heated in a water-bath at 55° for 3 minutes. The mixture is then kept overnight, when the yellow crystalline mass, which has separated, is collected and heated on a steam-bath with 20 c.c. of concentrated hydrochloric acid for 7 minutes. After cooling and keeping, the precipitate, consisting of the hydrochloride of *p*-nitrophenylhydrazine and sodium salts, is collected, dissolved in water, and treated with a concentrated solution of sodium acetate. *p*-Nitrophenylhydrazine separates —yield about 7—8 g.—light brown platelets from aqueous alcohol, m. p. 157° (dec.) (Bamberger and Kraus, *Ber.*, 1896, **29**, 1834; Davies, *J.*, 1922, **121**, 717).

(*b*) *Aliphatic Diazo-Compounds.*

Although the preparation of a diazotate of the formula $CH_3{\cdot}N{:}N{\cdot}OK$ has been described (Hantzsch and Lehmann, *Ber.*, 1902, **35**, 901; see p. 330), and some aliphatic diazocyanides and sulphites are known (E. Fischer, *Annalen*, 1879, **199**, 303; Wolff, *ibid.*, 1902, **394**, 41; v. Pechmann and Manck, *Ber.*, 1895, **28**, 2374), there appears to be no record of any aliphatic compound corresponding to the aryldiazonium salts having been isolated. Instead, the best-known and most accessible diazo-derivatives of the aliphatic series have the general formula $R\cdot CH{:}N_2$. (The following papers should be consulted for a discussion of the disposition of the nitrogen valencies and the structure of the diazo group in these compounds: Sidgwick, *J.*, 1929, 1108; Sidgwick, Sutton, and W. Thomas, *ibid.*, 1933, 406; Lindemann, Walter, and Groger, *Ber.*, 1930, **63**, 702.)

The preparation of diazo-paraffins, where R = H or alkyl, has been described on p. 330. The first member of this series, diazomethane, CH_2N_2, is a poisonous yellow gas, which is almost universally used in ethereal solution. Its homologues are in general more deeply coloured. Other diazo-compounds are diphenyldiazomethane, $Ph_2C{:}N$, phenyldiazomethane, $PhCH{:}N_2$, and diazofluorene,  $\begin{matrix}C_6H_4\\ |\\ C_6H_4\end{matrix}\!\!>C{:}N_2$. In addition to these are the diazo-esters such as diazoacetic ester, diazopropionic ester, etc., the general method of preparation of which has been described on p. 282. Some diazo-ketones are also known, such as diazoacetophenone, $Ph\cdot CO\cdot CH{:}N_2$.

All these diazo-compounds have a number of reactions in common. On treatment with dry organic acids or with dry hydrogen bromide or hydrogen chloride in non-hydroxylic solvents, nitrogen is evolved and the appropriate esters of the acids are formed (Curtius *J. pr. Chem.*, 1888, [ii], **38**, 413; v. Pechmann, *Ber.*, 1895, **28**, 857).

$$N_2{:}CH\cdot CO_2Et \begin{array}{l} \xrightarrow{CH_3\cdot CO\cdot OH} CH_3\cdot CO\cdot OCH_2\cdot CO_2Et + N_2 \\ \xrightarrow[HBr]{} BrCH_2\cdot CO_2Et + N_2 \end{array}$$

$$CH_2{:}N_2 \begin{array}{l} \xrightarrow{Ph\cdot CO_2H} CH_3\cdot O_2C\cdot Ph + N_2 \\ \xrightarrow[HCl]{} CH_3Cl + N_2 \end{array}$$

$$Ph\cdot CO\cdot CH{:}N_2 \xrightarrow[HO_2C\cdot H]{} Ph\cdot CO\cdot CH_2\cdot O_2C\cdot H + N_2$$

In the same way the action of dilute aqueous solutions of mineral acids results in the replacement of the nitrogen by hydroxyl, with the formation of a hydroxy-compound.

$$CH_2{:}N_2 + H_2O \qquad CH_3\cdot OH + N_2$$
$$N_2{:}CH\cdot CO_2Et + H_2O \qquad HO\cdot CH_2\cdot CO_2Et + N_2$$

A similar reaction occurs with phenols except that the catalytic action of mineral acids is not required.

$$Ph\cdot OH + CH_2{:}N_2 \qquad Ph\cdot OCH_3 + N_2$$

For the application of this reaction to the methylation of the phenols see p. 76.

The reaction of the diazoparaffins with alcohols takes place only slowly. Indeed, it is possible to keep an alcoholic solution of diazomethane for several days without the formation of any serious amount of ether. Diazoacetic ester, however, reacts with alcohols comparatively easily to give alkoxy-acetic esters.

A further reaction of diazomethane is the methylation of primary arylamines when the amine is added to an ethereal solution of the diazo-compound.

Diazo-compounds react with iodine or bromine in ethereal solution to yield nitrogen and a dihalogen compound

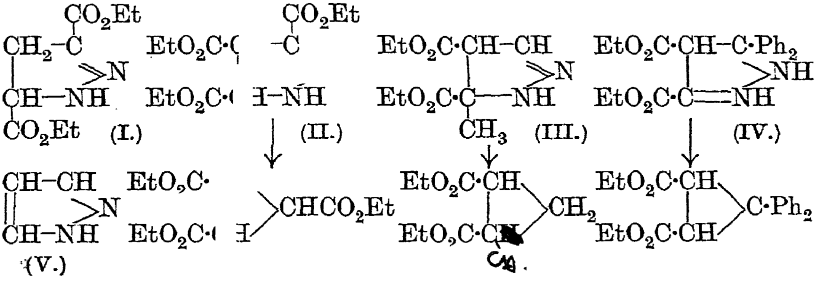
$$\mathrm{CH_2{:}N_2 + I_2 \longrightarrow CH_2I_2 + N_2}$$
$$\mathrm{EtO_2C{\cdot}CHN_2 + I_2 \longrightarrow EtO_2C{\cdot}CHI_2 + N_2}$$

The reaction of diazomethane with acyl chlorides is discussed on pp. 229, 230. The formation of diazo-ketones by this method appears to be a fairly general reaction, for benzoyl chloride reacts in the same way with diazoacetic ester to form benzoyldiazoacetic ester; phosgene reacts to give the mono-ester of diazomalonyl chloride.

$$\mathrm{2N_2{:}CH{\cdot}CO_2Et + Ph{\cdot}COCl \longrightarrow Ph{\cdot}CO{\cdot}C({:}N_2){\cdot}CO_2Et + ClCH_2{\cdot}CO_2Et}$$
$$\mathrm{2N_2{:}CH{\cdot}CO_2Et + COCl_2 \longrightarrow Cl{\cdot}CO{\cdot}C({:}N_2){\cdot}CO_2Et + ClCH_2{\cdot}CO_2Et}$$

Acetyl and propionyl chlorides react similarly (Staudinger, J. Becker, and Hirzel, *Ber.*, 1916, **49**, 1978; compare Staudinger, Anthes, and Pfenniger, *ibid.*, p. 1928).

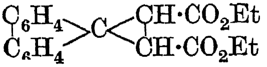
Diazomethane and diazoacetic ester combine additively with esters of the olefin carboxylic acids to form pyrazoline carboxylic acids. Thus acrylic ester gives (I) with diazoacetic ester; fumaric ester yields (II) (E. Buchner and co-workers, *Annalen*, 1892, **273**, 214).



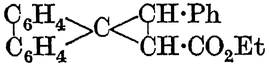
From diazomethane and citraconic ester (III) results (v. Pechmann and Burkard, *Ber.*, 1900, **33**, 3597), while diphenyldiazomethane and fumaric ester furnish (IV) (Staudinger, Anthes, and Pfenninger, *loc. cit.*).

Although ethylene, tolane, and stilbene do not combine with diazomethane, acetylene reacts to give pyrazole (V) (v. Pechmann, *Ber.*, 1898, **31**, 2950).

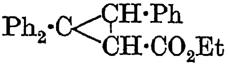
The pyrazoline esters formed by this reaction eliminate nitrogen on heating with the formation of derivatives of *cyclo*propane (Buchner, *loc. cit.*, p. 229). The reaction can be effected without isolating the intermediate pyrazoline, by heating the mixture of diazo-compound and unsaturated ester after the addition is complete. In this way diazofluorene and fumaric ester yield (VI); diazofluorene and cinnamic ester furnish (VII), while diphenyldiazomethane and cinnamic ester yield (VIII) (Staudinger and Gaule, *Ber.*, 1916, **49**, 1956; Staudinger, Anthes, and Pfenninger, *loc. cit.*).


$\begin{matrix}C_6H_4\\ C_6H_4\end{matrix}\!>C<\!\begin{matrix}CH\cdot CO_2Et\\ CH\cdot CO_2Et\end{matrix}$

(VI.)


$\begin{matrix}C_6H_4\\ C_6H_4\end{matrix}\!>C<\!\begin{matrix}CH\cdot Ph\\ CH\cdot CO_2Et\end{matrix}$

(VII.)


$Ph_2\cdot C<\!\begin{matrix}CH\cdot Ph\\ CH\cdot CO_2Et\end{matrix}$

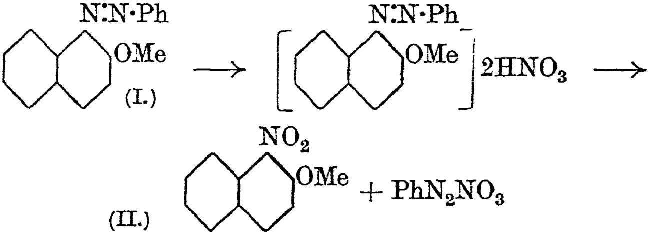
(VIII.)

The reduction of diazo-compounds under various conditions has been studied. The original papers should be consulted for details (Curtius and Jay, *J. pr. Chem.*, 1889, [ii], **39**, 31; *Ber.*, 1899, **27**, 775; Staudinger, Gaule, and Siegwart, *Helv. chim. Acta*, 1921, **4**, 212).

For some special reactions of diazoacetic ester, particularly its reaction towards alkalis, see papers by Curtius (*J. pr. Chem.*, 1888, [ii], **38**, 409) and Curtius, Daraspsky, and E. Müller (*Ber.*, 1908, **41**, 3161).

(2) *Azo-Compounds.*

Pure aromatic azo-compounds of the general formula R·N:N·R (where R = any aryl grouping) are coloured solids or liquids, and indifferent to dilute aqueous acids or alkalis. With concentrated mineral acids they form salt-like additive compounds which are decomposed on dilution. A number of such compounds has been obtained, such as azobenzene hydrofluoride, Ph·N:N·Ph,HF (Weinland and Reischle, *Ber.*, 1908, **41**, 3673), and azobenzene dihydrochloride, Ph·N:N·Ph,2HCl (Korczyński, *Ber.*, 1908, **41**, 4379; Baker, *J.*, 1907, **91**, 1500; compare also Fox and Hewitt, *J.*, 1908, **93**, 333; Hewitt and Pope, *Ber.*, 1897, **30**, 1624; Tuck, *J.*, 1907, **91**, 449). The intense colours which all azo-compounds develop in concentrated sulphuric acid is due also to salt formation (Hantzsch, *Ber.*, 1909, **42**, 2131), the acid presumably adding itself to the nitrogen of the azo-grouping. The shades of colour given by an azo-compound appear to depend on the nature of the aryl groups. Thus azobenzene and its hydroxy- and amino-derivatives yield deep golden colorations with concentrated sulphuric acid; αα-azonaphthalene and its derivatives furnish blue colours, while benzene azo-β-naphthols and its derivatives give red shades. The formation of such salts has been employed for the fission of suitable compounds. Thus the action of nitric acid (*d*, 1·48) on the methyl ether of benzene azo-β-naphthol (I) dissolved in ether yields the nitrate, which decomposes into benzenediazonium nitrate and α-nitro-β-naphthyl methyl ether (II) (Charrier and Ferreri, *Gazzetta*, 1913, **43**, ii, 148).



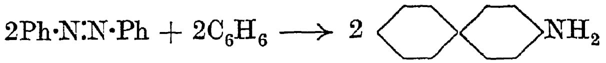
This provides a useful method of ascertaining the structure of azo-compounds where the normal method of reduction fails. The general method consists in adding the azo-compound to 10—20 times its weight of fuming nitric acid at room temperature. The azo-compound dissolves with change of colour, and after keeping for 10 minutes the solution is poured on ice. The precipitated nitro-compound is collected and the aqueous solution examined for the diazonium salt. The usefulness of this method is, however, restricted to alkylated aminoazo-compounds and to azo-ethers (Meldola and Morgan, *J.*, 1889, **55**, 608; Meldola and Hanes, *ibid.*, 1894, **65**, 841; compare Meldola and Southerden, *Proc.*, 1894, **10**, 118; O. Schmidt, *Ber.*, 1905, **38**, 3201). It does not give satisfactory results with simple azo-compounds such as azobenzene or azotoluene, nor does it appear to be satisfactory for *o*-substituted azo-compounds with the exception of those derived from β-naphthol.

1. *Oxidation of Azo-Compounds: Formation of Azoxy-Compounds.*—By the action of hydrogen peroxide or peracetic acid, azobenzene and some of its derivatives are oxidised smoothly to azoxy-compounds.

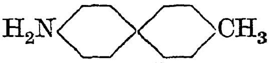
Preparation of Azoxybenzene.—An excess of 30% hydrogen peroxide is added to a solution of azobenzene in acetic acid. The precipitation of a portion of the azobenzene does not matter, as it redissolves slowly. After keeping for several days at room temperature, the red solution has become light yellow. It is then poured into water and the precipitated azoxybenzene collected, washed with water, and recrystallised from methyl alcohol. The reaction can be hastened by heating on a water-bath at 80—90° (Vanino, *Präparative Chemie*, Vol. II, p. 715; Angeli, *Über die Konstitution der Azoxy Verbindungen*).

2. *Fission of Azo-Compounds.*—The action of nitric acid on some azo-compounds has already been referred to. A less general reaction arises in their decomposition by hydrogen chloride. Thus azobenzene when boiled with hydrochloric acid yields a mixture of benzidine, aniline, and chloraniline. Some of the substituted azobenzenes behave similarly (compare Jacobson, *Annalen*, 1909, **367**, 304). Some aminoazo-compounds are also decomposed by heating with fuming hydrochloric acid (Wallach and Köllicker, *Ber.*, 1884, **17**, 395). It is noteworthy that azobenzene hydrochloride, when treated

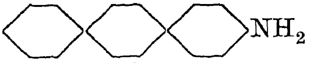
with aluminium chloride and benzene yields *p*-aminodiphenyl with about 10% of semidine and some aniline.



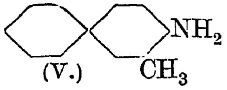
If the benzene is replaced by toluene or diphenyl, (III) and (IV) are formed, respectively. *o*-Azotoluene and benzene under similar conditions furnish (V) (Pummerer and Binapfl, *Ber.*, 1921, **54**, 2768; Pummerer, Binapfl, Bittner, and Schuegraf, *ibid.*, 1922, **55**, 3095).



(III.)



(IV.)

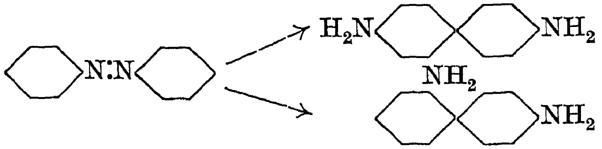


(V.)

The most generally applicable method of fission is by reduction of azo-compounds either with stannous chloride and hydrochloric acid or with " hydros."

$$\mathrm{Ph{\cdot}N{:}N{\cdot}Ph + 4H \qquad 2Ph{\cdot}NH_2}$$

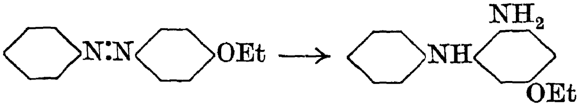
Using stannous chloride and hydrochloric acid, azobenzene, its homologues and many of its alkoxy-, halogen, and amino-substituted derivatives yield not only the normal products of fission, but also benzidine or its substituted products. This reaction has been the subject of a number of detailed investigations by Jacobsen and his co-workers, the results of which are summarised in the following paper: *Annalen*, 1922, **428**, 76. In addition to the normal products of fission, four different types of products have been obtained from azo-compounds of the benzene series. The principal reaction, except when there are substituents in both *para* positions, is the formation of a derivative of benzidine (VI).



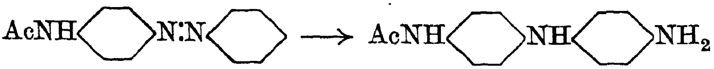
(VI.)

(VII.)

If one *para* position is occupied, an *ortho*-semidine is formed (VIII), while in rare cases a *para*-semidine is formed (IX).



(VIII.)



(IX.)

These changes are due to the intermediate formation of a hydrazo-compound, which undergoes rearrangement under the influence of acid. At the same time a variable amount of amine is formed by the fission of the hydrazo-compound. Thus azobenzene yields benzidine as the principal product with some diphenylin (VII) and aniline. Some azo-compounds such as 4 : 4′-diethoxyazobenzene or 2-aminoazobenzene or 2-hydroxyazobenzene undergo fission without the formation of any benzidine or semidine.

Reduction with stannous chloride and hydrochloric acid is of considerable value for determining the structure of azo-dyestuffs. With the majority of these, the reaction consists simply in the splitting of the molecule across the azo-grouping and the formation of two primary amines. For this purpose, a warm aqueous solution of the dyestuff is treated with stannous chloride in concentrated hydrochloric acid. When the solution is decolorised, the products are separated by whatever methods may be appropriate, such as steam distillation, filtration, extraction with ether, or the formation of quinoxalines (compare Witt, *Ber.*, 1888, **21**, 3471; 1886,

TABLE XXII.

Azo- and Azoxy-Compounds.

	M. p.	
Azoxybenzene	36°	Pale yellow.
2 : 2′-Azotoluene	55	Red.
o-Azoxytoluene	60	Yellowish.
p-Azoxytoluene	75	
Azobenzene	68	Orange-yellow.
4-Phenylaminoazobenzene	82	Golden yellow. HCl added to alc. sol. → violet coloration.
3 : 3′-Dichloroazoxybenzene	97	Pale ochre yellow.
3 : 3′-Dibromoazoxybenzene	111	
4-Dimethylaminoazobenzene	116	Yellow.
2 : 4-Diaminoazobenzene	118	Light yellow. Hydrochloride, dark grey crystals.
4-Aminoazobenzene	126	Yellow. Hydrochloride, blue violet needles.
o-Tolueneazo-β-naphthol	131	Red.
Benzeneazo-β-naphthol	134	Red.
p-Tolueneazo-β-naphthol	134	Red.
4 : 4′-Azotoluene	144	Orange-yellow.
4-Nitro-4′-phenylaminoazobenzene	151	Brown.
4-Chloro-4′-hydroxyazobenzene	151	
Benzeneazophenol	152	Orange. Sol. in alkalis.
4 : 4′-Dichloroazoxybenzene	155	
4-Bromo-4′-hydroxyazobenzene	155	
4-Chlorobenzeneazo-β-naphthol	162	Red.
4-Bromobenzeneazo-β-naphthol	172	Red.
4 : 4′-Dibromoazoxybenzene	172	
4-Amino-αα-azonaphthalene	173	Reddish-brown.
β-Naphthaleneazo-β-naphthol	176	Reddish-brown.
4-Methylaminoazobenzene	180	
4 : 4′-Dichloroazobenzene	183	Yellow.
αα-Azonaphthalene	190	Sol. in H_2SO_4 (conc.), blue.
3-Nitrobenzeneazo-β-naphthol	193	Orange.
4-Nitro-4′-aminoazobenzene	204	
4 : 4′-Dibromoazobenzene	204	Yellow.
2-Nitrobenzeneazo-β-naphthol	209	Light orange.
3-Nitro-4′-aminoazobenzene	212	Orange.
4-Nitro-4′-dimethylaminoazobenzene	230	
α-Naphthaleneazo-β-naphthol	229	Reddish-brown.
4-Nitrobenzeneazo-β-naphthol	249	Orange-brown.

19, 1721). Other reducing agents for this purpose are zinc dust and aqueous ammonia, or zinc dust and aqueous sodium hydroxide or titanous chloride.

A smooth process for the reductive fission of azo-compounds consists in the use of "hydros" (sodium hyposulphite, $Na_2S_2O_4$). The azo-compound dissolved in water or alcohol is treated with hydros in neutral or alkaline solution, till the colour is discharged. The subsequent operation depends on the nature of the products.

By mild reduction, preferably using zinc dust and aqueous alkali, simple azo-compounds are converted into hydrazo-compounds. Alkali and aluminium amalgam or sodium amalgam have also been used (Nölting and Fourneaux, *Ber.*, 1897, **30**, 2939).

CHAPTER X

HALOGEN COMPOUNDS

(1) General Characteristics.
(2) Elimination of the Elements of Halogen Hydride.
(3) Reduction.
    (*a*) Catalytic Methods.
    (*b*) Other Methods.
(4) Replacement of Halogen.
    (*a*) By Hydroxy Groups.
    (*b*) By Amino Groups.
(5) Reaction with Metals.
    (*a*) Formation of Organometallic Compounds.
        1. Organo-Magnesium Compounds.
        2. Organo-Zinc Compounds.
        3. Other Organometallic Compounds.
    (*b*) Reaction of Halogen Compounds with Organo-Magnesium Halides.
    (*c*) Union of Radicles of Halogen Compounds under the Influence of Metals.
(6) Reaction with Metal Salts.
    (*a*) Halides.
    (*b*) Cyanides.
    (*c*) Salts of Carboxylic Acids.
    (*d*) Nitrites.
    (*e*) Metal Derivatives of Malonic Esters, β-Keto Esters, and β-Diketones.
(7) Special Reactions.
    (*a*) Additive Reactions of Iodo-Compounds.
    (*b*) Isomerisation.

THIS chapter is restricted to a consideration of those reactions of the halogen-substituted hydrocarbons, alcohols, acids, etc., which are due to the presence of the halogen.

(1) *General Characteristics.*

The halogen-substituted hydrocarbons are in general non-electrolytes,* and sparingly soluble in water. Halogen compounds containing other characteristic groupings, such as $-CO_2H$, $-OH$, $>CO$, exhibit not only the reactions due to these groupings, but also the general characteristics of the halogen in halogen-substituted hydrocarbons, such as the replacement of the halogen by groupings such as $-OH$, $-OAlk$, $-OAr$, $-NO_2$, $-NH_2$, etc., and also the elimination of the elements of halogen hydride. Such reactions are, however, often modified by the presence of other groupings.

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* Solutions of the triphenylmethyl halides in liquid sulphur dioxide are conducting. On the other hand, solutions of alkyl halides in liquid sulphur dioxide are non-electrolytes (Walden, *Z. phys. Chem.*, 1903, **43**, 454; Schlenck, Weickel, and Herzenstein, *Annalen*, 1910, **372**, 11).

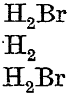
The reactivity of the halogen appears to be dependent on a number of factors, among which are: (1) the nature of the halogen, (2) the nature of the adjacent groups, (3) the type of linkages joining the rest of the molecule to the carbon carrying the halogen. This latter is of considerable importance. The following table illustrates the effect of lengthening the chain of the alkyl halides. It gives comparative values of the reactivity of the alkyl halides. These values are obtained from reaction with a variety of reagents and illustrate the effect of using different reagents.

	(1).	(2).	(3).	(4).	(5).	(6).	(7).	(8).
Methyl	572	42	—	1150	1129	935	1500	7785
Ethyl	100	100	100	100	100	100	100	100
n-Propyl	39	47	135	40	14	24	31	24
*iso*Propyl	36	103	171	23	1	8	—	—
n-Butyl	37	31	60	28	14	—	—	—
*iso*Butyl	15	7	171	37	1	4	—	—
sec.-Butyl	—	—	305	—	—	—	—	—
*iso*Amyl	19	27	—	14	—	—	—	—
sec.-Hexyl	33	—	—	41	—	—	—	—
n-Heptyl	34	—	—	—	14	—	—	—
n-Octyl	33	—	—	—	14	—	—	—
sec.-Octyl	34	—	—	31	—	—	—	—
Cetyl	32	—	—	—	—	—	—	—

(1) NaOPh in alcoholic solution (Segaller, *J.*, 1914, **105**, 106).
(2) $AgNO_3$ in alcohol (Burke and Donnan, *J.*, 1904, **85**, 555).
(3) Formation of olefin by the action of alcoholic potash at 78° (Brussof, *Z. phys. Chem.*, 1900, **34**, 129).
(4) $NaOCH_2Ph$ in alcoholic solution (Haywood, *J.*, 1922, **121**, 1904).
(5) Reaction with triethylamine in acetone at 100° (Menschutkin and Wassilieff, *Z. phys. Chem.*, 1890, **5**, 589).
(6) Reaction with sodioacetoacetic ester in alcohol (J. Wislicenus, *Annalen*, 1882, **212**, 244).
(7) Reaction with dimethylaniline (R. W. D. Preston and H. O. Jones, *J.*, 1912, **101**, 1930).
(8) Reaction with tri*iso*amylamine (R. W. D. Preston and H. O. Jones, *loc. cit.*).

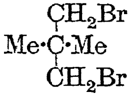
The effect of the nature of the carbon linkages is seen by comparing the alkyl halides with the aryl halides. The former are comparatively reactive, while the latter are unacted on by aqueous or alcoholic alkalis or ammonia at 100°, and neither do they react with alcoholic silver nitrate, or alkali cyanides at 100°. The mobility of the halogen is, however, greatly influenced by the presence of substituents in the nucleus (see p. 54). Aliphatic halogen compounds containing the grouping $>C{:}\overset{|}{C}\cdot Hal$ appear to be intermediate in reactivity between that of the alkyl halides and the aromatic halogen compounds.

Comparatively slight changes in the structure may have a profound effect on the reactivity of the halogen. Thus trimethylene dibromide (I) reacts normally with aqueous sodium carbonate to give a glycol; with potassium cyanide to yield a dinitrile; with silver or potassium acetate to give a diacetate. Its ββ-dialkyl derivatives (II), (III), and (IV) are surprisingly stable to these reagents. Boiling aqueous sodium carbonate has no action on (III) after 33 hours, while 90% of (II) is recovered unchanged after being heated with aqueous sodium carbonate in a sealed tube at 150°. It is unchanged by boiling with aqueous alcoholic potassium cyanide. In contrast (V) reacts fairly easily with aqueous sodium carbonate, 88% of the bromine being replaced after 7 hours; after 11 hours.



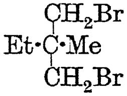
$$\begin{array}{c} H_2Br \\ \cdot H_2 \\ H_2Br \end{array}$$

(I.)



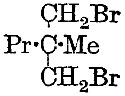
$$\begin{array}{c} CH_2Br \\ Me\cdot C\cdot Me \\ CH_2Br \end{array}$$

(II.)



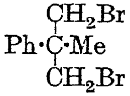
$$\begin{array}{c} CH_2Br \\ Et\cdot C\cdot Me \\ CH_2Br \end{array}$$

(III.)



$$\begin{array}{c} CH_2Br \\ Pr\cdot C\cdot Me \\ CH_2Br \end{array}$$

(IV.)



$$\begin{array}{c} CH_2Br \\ Ph\cdot C\cdot Me \\ CH_2Br \end{array}$$

(V.)

(2) *Elimination of the Elements of Halogen Hydride.*

When an aliphatic halogen compound containing the grouping $>CH\cdot Cl$ enters into reaction with any reagent capable of combining with or reacting with halogen hydride, there is the possibility of the replacement of the halogen being accompanied by the formation of an unsaturated compound. It thus happens that, in attempting to replace the halogen, a greater or smaller amount of unsaturated compound may result, if the structure of the halogen compound is favourable. Under comparable experimental conditions, the tendency to formation of unsaturated compounds is greatest when the halogen is attached to a tertiary carbon atom, and least when it is attached to a primary one. This is illustrated by the behaviour of *tert.*-butyl iodide. By the action of silver iodide, silver cyanide, ammonia, or silver cyanate or the alkali metal derivatives of acetoacetic or malonic esters, the principal product is butylene, little or no substitution occurring. When the same reagents act on the isomeric *n*- or *iso*-butyl halides, however, the chief reaction is the replacement of the halogen.

The extent to which the unsaturated compound is formed from substance behaving normally to substituting reagents depends also on the experimental conditions. It is generally possible to select such conditions that either substitution or olefin formation chiefly results.

The conditions for the replacement of halogen by hydroxyl are discussed in a subsequent section (p. 369). The most favourable yields of hydroxy-compound are generally obtained by the hydrolysing action of feebly alkaline solutions. If the alkali concentration is increased, the yield of olefin tends to increase at the expense of the hydroxy-compound. Concentrated alcoholic potash is generally more effective than aqueous alkali for this purpose, and is often used for the preparation of olefins from alkyl halides and of unsaturated compounds in general. There is, however, the disadvantage that ethers may be formed. Thus *n*-propyl bromide gives about 20% of the theoretical yield of propylene and 60% of *n*-propyl ethyl ether. *iso*Propyl bromide under similar conditions yields about 75% of propylene. *tert.*-Butyl iodide or chloride, however, furnish butylene only (Nef, *Annalen*, 1899, **309**, 126). In spite of its limitations, this method has frequently been used for the preparation of unsaturated compounds.

Preparation of iso*Butylene.*—*tert.*-Butyl iodide (40 g.) is gradually added from a tap funnel to a solution of 20 g. of potassium hydroxide in 60 g. of 90% alcohol to which have been added 10 g. of solid potassium hydroxide. The butylene which is evolved is passed through a washing system containing water and dilute alkali, and dried by passage through calcium chloride (compare Butleroff, *Ber.*, 1870, **3**, 422, 623).

Preparation of β-Bromobutylene.—βγ-Dibromobutane (10 g.) is mixed with 25 g. of 20% alcoholic potash. Heat is evolved and the reaction is completed by heating under reflux for ¾ hour. The product is precipitated as a colourless oil by the addition of water to the reaction mixture. It is separated, dried over calcium chloride, and distilled, b. p. 88—92° (J. Wislicenus, Talbot, and Henze, *Annalen*, 1900, **313**, 237).

Preparation of Phenylacetylene.—ω-Bromostyrene (100 g.) is added at the rate of something less than 1 drop a second to 150 g. of potassium hydroxide contained in a 500-c.c. distillation flask fitted with a condenser and heated to 200° in an oil-bath. Phenylacetylene distils over. During the course of the reaction the temperature of the oil-bath is gradually raised to 215—220°, and is kept at this point till all the bromostyrene has been added. It is then maintained at 230° till nothing more distils over. The distillate consists of crude phenylacetylene and water. The upper layer is separated, dried over solid potash, and distilled, b. p. 142—144°—yield 37 g. (Hessler, *Organic Syntheses*, 1922, **2**, 67).

Tertiary amines such as quinoline, dimethylaniline, trimethylamine, or pyridine have been employed for the production of olefins. Thus some *tert.*- and *sec.*-aryl alkyl chlorides yield olefins by heating with pyridine at 120—130° (Klages, *Ber.*, 1904, **37**, 1451).

Preparation of $\Delta^{1:3}$-cyclo*Hexadiene.*—1 : 2-Dibromo*cyclo*hexane (42 g.) and freshly distilled quinoline (90 g.) are heated together in a long-necked distillation flask attached to a condenser, a thermometer being placed in the liquid. The reaction sets in at 160° and becomes marked at 178°. When it has ceased, the temperature of the liquid is kept at 185—190° for 10 minutes. The thermometer is then raised from the liquid and the mixture heated till all the liquid boiling below 100° has passed over.

A second portion of 42 g. of the dibromide is treated in exactly the same way. The combined distillates (22 g.) are distilled again from quinoline. The resulting distillate is washed with dilute sulphuric acid, dried with calcium chloride, and then fractionated several times over sodium. *cyclo*Hexadiene distils over at 81·5—82° (Crossley, *J.*, 1904, **85**, 1416).

The position of the double bonds in unsaturated compounds produced by the action of quinoline on *cyclo*hexylmethyl halides is uncertain, for quinoline salts appear to be able to cause migration of the double linking (Faworski and Borgmann, *Ber.*, 1907, **40**, 4870).

For other examples of the use of quinoline in the preparation of unsaturated compounds see papers by Baeyer (*Annalen*, 1894, **278**, 94, 107) and Markovnikoff (*ibid.*, 1898, **302**, 27).

(3) *Reduction of Halogen Compounds.*

A survey of the different methods used for the replacement of halogen by hydrogen shows that they can be divided into two broad groups: (1) those employing molecular hydrogen in conjunction with a catalyst; (2) those using metals usually in presence of acetic acid, alcohol, or water.

(a) *Catalytic Methods.*—In the majority of the published descriptions of this type of reduction, the essential operations consist in diluting the halogen compound with alcohol or water, and then, after adding the appropriate catalyst, pumping in hydrogen until the required amount has been taken up. The reduction is effected very conveniently in a hydrogenation flask, and the technique is similar to that used in the hydrogenation of unsaturated compounds. An alkali or an inorganic carbonate is usually introduced into the mixture to combine with the halogen hydride liberated during the reduction. Platinum or palladium have been largely used as catalysts, although nickel has also been successfully employed. Busch and Stöve (*Ber.*, 1916, **49**, 1063), employing palladium deposited on calcium carbonate, have used the method for the quantitative determination of halogen in a variety of compounds such as iodobenzene, bromobenzoic acid, and aliphatic halogen compounds. Busch and Stöve's technique has also been used for preparative purposes. Rosenmund and Zetsche (*Ber.*, 1918, **51**, 578) use platinum or palladium deposited on barium sulphate or some other indifferent support in presence of alkali for the dehalogenation of such compounds as dibromosuccinic acid and bromobenzoic acid. With this method, crotonic acid is formed from chlorocrotonic acid, although phenylpropionic acid is obtained from *o*-chlorocinnamic acid. Kelber (*Ber.*, 1917, **50**, 305; compare *ibid.*, 1921, **54**, 2255) finds that many aliphatic and aromatic halogen compounds are quantitatively reduced in aqueous alcohol containing some alkali by hydrogen in presence of finely-divided nickel. This method is recommended for the estimation of halogen. The reduction may sometimes take an abnormal course. Thus benzotrichloride ($Ph{\cdot}CCl_3$) is converted into tetrachloro-αβ-diphenylethane (VI) by hydrogenation in presence of colloidal palladium; while benzal chloride yields some toluene and αβ-dichloro-αβ-diphenylethane (VII) under similar conditions (Borsche and Heimbürger, *Ber.*, 1915, **48**, 452).

(VI.) $Ph{\cdot}CCl_2{\cdot}CCl_2{\cdot}Ph$ $Ph{\cdot}CHCl{\cdot}CHCl{\cdot}Ph$ (VII.)

(b) *Other Methods.*—A convenient process for the reduction of the lower alkyl iodides to the corresponding paraffins consists in allowing the alkyl iodide containing some alcohol to react with a zinc–copper couple (Gladstone and Tribe, *J.*, 1873, **26**, 445, 678, 961). This method is frequently employed for the laboratory preparation of methane and ethane. The gases so prepared usually contain a small quantity of hydrogen (compare Campbell and Parker, *J.*, 1915, **103**, 1292). For the reduction of some of the highe alkyl halides, zinc dust and hydrochloric acid have been used sucess fully (L. Clarke, *J. Amer. Chem. Soc.*, 1909, **31**, 113; 1908, **30** 1147). Other methods for the reduction of saturated monohaloge compounds include zinc dust and alcohol; palladised zinc an hydrochloric acid (Zelinsky, *Ber.*, 1901, **34**, 2801; 1898, **31**, 3203) amalgamated aluminium (H. Wislicenus, *J. pr.* Chem., 1896, [ii] **54**, 52).

The smooth formation of hydrocarbons from halogen-substitute hydrocarbons can be achieved through the intermediate formatio of the Grignard reagent (see p. 374), which on treatment with wate or dilute acid yields the hydrocarbon according to the followin equation:

$$\text{R}\cdot\text{MgI} + \text{H}_2\text{O} \longrightarrow \text{RH} + \text{HO}\cdot\text{MgI}$$

When two halogens are attached to adjacent carbon atoms, th usual action of zinc and acetic acid or alcohol or of sodium o magnesium is to eliminate the halogens with the formation of a unsaturated compound.

$$>\text{CBr}\cdot\text{CBr}< \;\longrightarrow\; >\text{C}{:}\text{C}<$$

This is a valuable method for the preparation of pure unsaturated compounds, inasmuch as they can be isolated or purified through their dibromides or dichlorides, and subsequently reconverted into the original unsaturated compound. Thus propylene dibromide heated in a water-bath with zinc and water readily yields propylene (Linnemann, *Ber.*, 1877, **10**, 1113). A similar effect is produced by treating alkylene dibromides with zinc filings in moist ether. This method can also be applied to some dibromo-aliphatic acids (Michael, *Ber.*, 1901, **34**, 4217 *et seq.*; Michael and Schulthess, *J. pr. Chem.*, 1891, [ii], **43**, 589). The use of zinc and alcohol for the reduction of dibromo-compounds to unsaturated compounds is illustrated by the following descriptions.

Preparation of Butadiene.—The apparatus used for this preparation consists of a round-bottomed flask attached to a Soxhlet which carries an efficient reflux condenser. A mixture of 200 g. of zinc dust and 250 c.c. of absolute alcohol is placed in the flask and 100 g. of butadiene tetrabromide in the thimble of the Soxhlet. The tetrabromide is extracted by the alcohol as it refluxes from the condenser and then reduced by the zinc dust in the flask. The butadiene which is liberated is led through a spiral condenser cooled by an efficient freezing mixture and then collected in a bottle or tube similarly cooled. Alternatively, the vapour may be condensed in a suitable solvent. The yield is about 80—90%, b. p. − 5° to − 4° (Thiele, *Annalen*, 1899, **308**, 339).

Preparation of 1 : 4-*Dihydronaphthalene.*—12·6 G. of 2 : 3-dibromo-1 : 4-dihydronaphthalene are added all at once to 21 g. of zinc filings covered by 100 c.c. of absolute alcohol at 30°. Reaction soon commences and the temperature rises to about 65°. The mixture is maintained at 50—65° till a test portion shows that the dibromide has disappeared. The solution is then decanted from the metal, diluted with water, and the oil which is thus precipitated taken up in ether. After washing with brine solution to remove the alcohol, the ethereal solution is dried and evaporated. The residue consists of pure 1 : 4-dihydronaphthalene, m. p. 24—25°—yield 5·4 g. (Strauss, *Ber.*, 1913, **46**, 1054).

Zinc and alcohol have also been applied to the debromination of αβ-dibromosuccinic ester (Michael and Schulthess, *loc. cit.*) and to the preparation of acetylenes from bromoethylenes of the general formula Alk.CBr⁚CHBr (Lespieau, *Bull. Soc. chim.*, 1921, [iv], **29**, 532). For the use of zinc and acetic acid and for abnormal course of the reaction the following papers should be consulted: Brand, *Ber.*, 1921, **54**, 1987; Brand and Kercher, *ibid.*, p. 2007. Sodium and moist ether have been employed for the preparation of acetylenes from the corresponding dichlorides (Kunckell and Gotsch, *Ber.*, 1900, **33**, 2656; Kunkell and Koritsky, *ibid.*, p. 3261).

According to v. Braun and Kirschbaum (*Ber.*, 1921, **54**, 604) the use of zinc filings and alcohol may cause polymerisation of the resulting olefin. They recommend the action of magnesium on an ethereal solution of the dibromide as a more satisfactory alternative. Examples of this application are given by v. Braun and Moldänke (*Ber.*, 1921, **54**, 618) and by v. Braun and Lemke (*ibid.*, 1923, **56**, 1563).

A very elegant method due to Finkelstein (*Ber.*, 1910, **43**, 1530) is based on the fact that though the dichlorides and dibromides derived from the olefins are generally stable, many of the corresponding di-iodides eliminate iodine with the formation of the olefin. Consequently, by treating such dibromides and dichlorides with sodium iodide in acetone solution, the olefin results (see p. 381). Thus ethylene is obtained from ethylene dibromide; cinnamic acid dibromide furnishes cinnamic acid; dibromosuccinic acid gives fumaric acid; αβ-dibromopropionic acid yields acrylic acid (Finkelstein, *loc. cit.*; Biilmann, *Rec. trav. chim.*, 1917, **36**, 313; 1917, **37**, 245).

(4) (a) *Replacement of Halogen by Hydroxy-Groups.*—Hydrolysis of *n*- and *sec.*-alkyl halides can be achieved by heating with an excess of water in sealed tubes at 100° higher.

$$R{\cdot}CH_2{\cdot}Hal + H_2O \longrightarrow R{\cdot}CH_2{\cdot}OH + HHal$$

tert.-Alkyl halides are more easily hydrolysed. They readily yield the corresponding alcohol with smaller or greater amounts of olefin by heating with water under reflux for a short time. So easily are the bromides and iodides attacked that they may be estimated fairly accurately in mixtures with *sec.*- and *n*-alkyl halides by this means. Titration of the liberated halogen hydride furnishes a direct measure of the *tert.*-alkyl halide (Michael and Leupold, *Annalen*, 1911, **379**, 287). Triarylmethyl halides are also smoothly converted into the corresponding alcohols by the action of warm water.

For the preparation of alcohols from *n*- and *sec.*-halides, it is more convenient to use aqueous alkaline solutions, such as dilute solutions of alkali hydroxides, lime water, baryta water, or alkali carbonates. Where there is a marked tendency to form an olefin, an aqueous suspension of lead oxide or silver oxide has been used. It is sometimes advisable (in order to avoid olefin formation) to convert the halide into the acetate of the corresponding alcohol by reaction with silver acetate or potassium acetate and subsequently to hydrolyse the ester. This procedure is frequently adopted for the preparation of glycols from dibromides.

The replacement of halogen in the aromatic nucleus by hydroxyl takes place only with considerable difficulty, unless there are nitro-groups also present in the nucleus (see p. 54). Thus chlorobenzene is unchanged by heating with an excess of aqueous alkali at 200°. At 300° an almost quantitative yield of sodium phenate results by the action of an excess of 15—20% aqueous alkali (K. H. Meyer and Bergius, *Ber.*, 1914, **47**, 3155). According to Rosenmund and Harms (*ibid.*, 1920, **53**, 2226) phenols may be obtained by heating the appropriate aryl halide with crystalline sodium acetate and copper bronze at about 220—250° in sealed tubes.

Preparation of Ethylene Glycol.—A mixture of 94 g. of ethylene dibromide and a solution of 69 g. of potassium carbonate in 500 c.c. of water is heated under reflux till the oily dibromide has disappeared (1—2 days). The water is evaporated under reduced pressure at 50° and the dry residue extracted twice with absolute alcohol. The filtered alcoholic extracts are evaporated under reduced pressure and the residue fractionated at atmospheric pressure. The distillate up to 110° is rejected. Between 170° and 200° crude glycol is collected. The intermediate fractions are refractionated to furnish a further quantity of crude glycol. Distillation of the crude product yields the pure glycol, b. p. 195—197°—yield about 10 g.

Preparation of o-*Nitrobenzyl Alcohol.*—A mixture of 10 g. of *o*-nitrobenzyl chloride, 150 c.c. of water, and 8 g. of potassium carbonate is boiled under reflux for 4 hours. *o*-Nitrobenzyl alcohol is obtained as a mass of needle-like crystals on cooling. It is collected by filtration, dried on porous earthenware, and crystallised from benzene, m. p. 74°—yield about 5 g. (Söderbaum and Widman, *Ber.*, 1892, **25**, 3290).

Preparation of Triphenyl Carbinol.—Triphenyl methyl chloride is boiled with an excess of water for 10 minutes. The carbinol is then collected by filtration and crystallised from hot ethyl alcohol, m. p. 162°.

Preparation of Glycollic Acid.—A solution of 200 g. of chloracetic acid in 1400 c.c. of water is heated on a water-bath with an excess of barium carbonate (about 400 g.) till there is no further solution of the carbonate. The volume of the solution should be kept approximately constant by adding water at intervals. When the hydrolysis is complete, the unchanged carbonate is filtered off and the filtrate treated with the exact amount of dilute sulphuric acid needed to precipitate all the barium. After collecting the barium sulphate by filtration, the filtrate is concentrated to a syrup on the water-bath. Crystallisation is initiated in the cooled syrup by adding a crystal of glycollic acid. The crystalline mass is subsequently drained and then exposed to the air till free from hydrochloric acid. It is finally purified by crystallisation from a small quantity of water, m. p. 78° (Witzemann, *J. Amer. Chem. Soc.*, 1917, **39**, 110).

Preparation of α-Hydroxypalmitic Acid.—Crude α-bromopalmitic acid (105 g.) is added to a solution of 75 g. of potassium hydroxide in 900 c.c. of water and the solution then maintained at its boiling point for 10 hours by passing superheated steam into it. Crude α-hydroxypalmitic is precipitated from this solution by adding an excess of dilute sulphuric acid. The acid is taken up in ether, and after washing the ethereal solution with water and drying it over calcium chloride, the solvent is evaporated. Crystallisation of the residue from chloroform furnishes pure α-hydroxypalmitic acid, m. p. 87°—yield 67 g. (Le Sueur, *J.*, 1905, **87**, 1895).

α-Hydroxypentadecylic and α-hydroxymyristic acids are similarly prepared.

(b) *Replacement of Halogen by Amino-Groups.*—As the reaction of alkyl halides with amines is considered in Chapter VII, the subject matter of the present section is restricted to the behaviour of ammonia with alkyl halides, except where it is considered necessary to compare the behaviour of ammonia with amines. Reaction of the alkyl halides with ammonia furnishes a method for the preparation of alkylamines. The replacement is represented by equation 1. It is obvious that the halogen hydride formed in the reaction will be distributed between the ammonia and the primary amine. Accordingly, reaction will also proceed between the alkyl halide and the free alkylamine now present in the mixture giving a dialkylamine (equation 2). This will in turn also yield successively a tertiary amine and a quaternary ammonium salt. The product of the action of ammonia on an alkyl halide may therefore consist of a mixture of primary, secondary, tertiary amines and a quaternary ammonium salt.

$$\begin{array}{rll} RI + NH_3 & RNH_2 + HI & (1) \\ RI + R{\cdot}NH_2 & R_2NH + HI & (2) \\ RI + R_2{\cdot}NH & R_3N + HI \; . & (3) \\ RI + R_3N & R_4NI \; . \; . \; . & (4) \end{array}$$

The relative proportions of each of these products are dependent not only on the relative amount of the original reactants and on the relative strengths of the amines produced, but also on the rate with which each reacts with alkyl iodide.

In general, the reaction between ammonia and an alkyl halide is effected by heating the reactants in alcoholic solution at 100° in sealed tubes, or in an autoclave, or by keeping the mixture of ammonia and alkyl halide at room temperature.

The application of this method is restricted by the tendency of *sec.*- and *tert.*-alkyl halides to split out the elements of halogen hydride. Thus *sec.*-propyl iodide yields a mixture of *sec.*-propylamines and propylene by reaction with ammonia at 100°. *sec.*-Hexyl and *sec.*-octyl iodides behave similarly (Jahn, *Ber.*, 1882, **15**, 1288). *cyclo*Hexyl halides are converted into *cyclo*hexene by treatment with ammonia. There appears to be no record of *cyclo*hexylamine having been prepared in this way. Even primary arylamines, which are generally less efficient in causing the formation of olefins from halogen compounds, yield a notable proportion of *cyclo*hexene from *cyclo*hexyl bromide together with the corresponding *cyclo*hexyl arylamine (Hickinbottom, *J.*, 1932, 2650). Olefins are also formed when *tert.*-alkyl halides react with ammonia (Nef, *Annalen,* 1899, **309**, 164; A. W. Hofmann, *Ber.*, 1874, **7**, 513). With aniline a small yield of *tert.*-alkylaniline is obtained, but even here olefin is the principal product (Nef, *loc. cit.*; Hickinbottom, *J.*, 1933, 946).

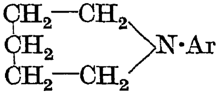
The tendency for *sec.*- and *tert.*-halides to yield olefins rather than to suffer replacement is seen also with the dihalogen paraffins. Thus while ethylene dibromide or dichloride, and trimethylene and propylene dibromides react normally with alcoholic ammonia with the formation of the corresponding diamines, βγ-dibromobutane furnishes β-bromo-Δ^{β}-butene as the principal product of the action of ammonia at 110°, only a small proportion of βγ-diaminobutane being formed (Morgan and Hickinbottom, *J.S.C.I.*, 1924, **43**, 310T). Replacement of both halogens of βγ-dibromobutane proceeds normally by reaction with arylamines (Morgan and Hickinbottom, *J.*, 1923, **123**, 97).

Preparation of Ethylenediamine.—Ethylene dichloride (42 g.) and 510 c.c. of concentrated aqueous ammonia (33%) are heated in an autoclave at 115—120° for 5 hours. The product is then evaporated till crystallisation commences, when three times its bulk of alcohol is added. The crystals which separate are collected and washed with alcohol. A further quantity of crystalline material is obtained by evaporating the mother-liquor. The yield of ethylenediamine hydrochloride thus obtained is about 50 g.

Ethylenediamine is obtained from it by mixing it into a paste with finely-powdered sodium hydroxide and then distilling. The hydrate, b. p. 118°, distils over (Kraut, *Annalen*, 1882, **212**, 253).

Fargher (*J.*, 1920, **117**, 1351) has investigated the by-products of this reaction, and has shown that they consist of diethylenetriamine and triethylenetetramine (compare Hofmann, *Proc. Roy. Soc.*, 1860, **10**, 619; *Ber.*, 1890, **23**, 3712).

Polymethylene dibromides, with the halogens in 1 : 4 and 1 : 5 positions, show a marked tendency towards the formation of cyclic compounds by reaction with ammonia and amines. Thus 1 : 5-dibromopentane reacts with arylamines to form aryl-substituted piperidines (VIII); 1 : 4-dibromopentane similarly yields methylpyrrolidines (IX). The presence of substituents in the aryl amine, *ortho* to the amino-group, hinders this reaction, and the products are then 1 : 4- and 1 : 5-diamines (v. Braun, *Ber.*, 1908, **41**, 2158; Scholtz and Friemehlt, *ibid.*, 1899, **32**, 848; v. Braun, *ibid.*, 1904, **37**, 3210). The effect of the type of amine is best illustrated by the behaviour of *o*-xylylene dibromide (X). With ammonia, reaction occurs giving the dicyclic ammonium salt (XI). Primary aromatic amines yield compounds of the type (XII), but aromatic amines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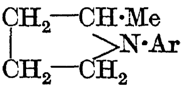
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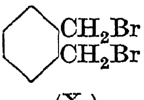
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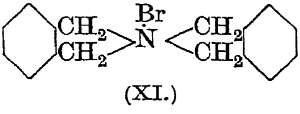
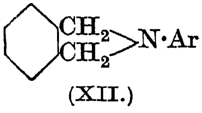

(XI.)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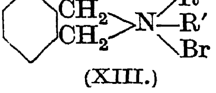
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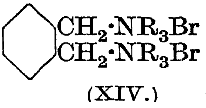

(XIV.)

substituted in the *ortho* position form diamines. A quaternary ammonium salt of the type (XIII) is the principal product from secondary amines. Tertiary aliphatic amines furnish diquaternary ammonium salts (XIV), but tertiary aromatic amines do not usually react.

Of the halogen-substituted fatty acids only the α-substituted products easily suffer normal replacement by the action of ammonia and amines.

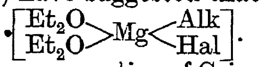
Preparation of α-Aminocaproic Acid.—150 G. of α-bromocaproic acid are slowly added to 850 c.c. of aqueous ammonia (*d*, 0·9) contained in a stout round-bottomed flask. The flask is stoppered and kept for 20—30 hours at 50—55°. During this period the greater part of the amino-acid has crystallised out. It is collected by filtration and washed with methyl alcohol. The aqueous filtrate is evaporated almost to dryness and then treated with 200 c.c. of methyl alcohol. A further crop of α-aminocaproic acid is thus obtained. It is purified by washing with methyl alcohol to remove ammonium bromide and crystallised from water—yield 63—68 g. (Marvel and Vigneaud, *Organic Syntheses*, 1925, **4**, 3).

Preparation of Glycine.—A solution of 189 g. of chloracetic acid in 8 litres of aqueous ammonia (*d*, 0·90) is kept at room temperature for 48 hours. The excess of ammonia is distilled off and the solution concentrated under reduced pressure till the precipitation of ammonium chloride commences. The salt is redissolved by the addition of a small amount of water and then filtered to remove suspended matter. The filtrate, which should have a volume of about 500 c.c., is mixed with 800 c.c. of methyl alcohol and 140 c.c. of pyridine. Crystallisation of glycine commences almost immediately. It is kept overnight and then filtered (yield 96 g.). It is purified by solution in 300 c.c. of warm water, decolorised with charcoal, and after filtration 800 c.c. of methyl alcohol are added. Yield of pure glycine, m. p. 225—230°, is 80 g. (Boutwell and Kuick, *J. Amer. Chem. Soc.*, 1930, **52**, 4166; compare G. R. Robertson, *ibid.*, 1927, **49**, 2892).

(5) *Reaction of Halogen Compounds with Metals.*

(a) *Formation of Organometallic Compounds.* (1) *Organomagnesium Compounds.*—Alkyl and aryl halides—in particular bromo- and iodo-compounds—react with magnesium in presence of ether to form compounds of the type R·Mg·Hal which are soluble in ether. For the purposes of further reactions ethereal solutions of the organomagnesium halides are used (Grignard, *Compt. rend.*, 1900, **130**, 1322; *Ann. Chim. Phys.*, 1901, **24**, [vii], 433).

Evaporation of the solvent from ethereal solutions of Grignard reagents leaves a residue of alkylmagnesium halide associated with 1 or 2 molecular proportions of ether. A number of different formulæ have been proposed to account for this combination between ether and the organomagnesium halide (Baeyer and Villiger, *Ber.*, 1902, **35**, 1202; Tschelinzeff, *ibid.*, 1906, **39**, 773, 1674, 1682, 1686; Hess and Rheinboldt, *ibid.*, 1921, **54**, 2043; Jolibois, *Compt. rend.*, 1912, **155**, 353). Meisenheimer and Caspar (*Ber.*, 1921, **54**, 1655) have suggested that they are co-ordination compounds of the type



$\left[\begin{matrix}Et_2O\\Et_2O\end{matrix}\!>Mg<\!\begin{matrix}Alk\\Hal\end{matrix}\right]$.

The preparation of Grignard compounds is illustrated by the following general description.

A weighed amount of clean dry magnesium turnings (1 mol. proportion) is introduced into the reaction flask, which has been previously dried at 110°. The flask is fitted with an efficient reflux condenser and a dropping funnel, the upper ends of both being fitted with guard tubes containing anhydrous magnesium perchlorate. A small volume of ether and a crystal of iodine are added to the magnesium, and then a small volume of the alkyl halide. If the reaction does not start at room temperature the contents of the flask are warmed to 45°. As soon as the initial reaction shows signs of subsiding, the alkyl halide (1 mol. proportion) diluted with 1—3 volumes of ether is added regularly and slowly from the tap funnel. When no further action appears to take place, the mixture is refluxed gently till no more magnesium dissolves.

The magnesium used for this reaction must be perfectly clean and free from oil. It is now possible to obtain magnesium turnings which conform to these requirements from the usual dealers in laboratory chemicals. If there is any doubt about the cleanliness of the metal, it should be washed two or three times with ether and dried under reduced pressure at 78°.

The ether used must be free from alcohol. Ordinary commercial ether must be purified by washing several times with brine, and then stored for several days over calcium chloride before distilling it. It is finally dried by keeping in contact with sodium wire for several days and then distilled over a small amount of bright sodium. Immediately before use it is distilled over a small amount of phosphorus pentoxide. It is more convenient, however, to use purified commercial ether (*d*, 0·720) and to distil it over phosphorus pentoxide as required.

In preparing the Grignard reagent, it is preferable to use a flask fitted with a mercury sealed stirrer, otherwise the flask must be shaken at frequent intervals during the reaction (Gilman, Zoellner, and Dickey, *J. Amer. Chem. Soc.*, 1929, **51**, 1579; compare Wren, *Organometallic Compounds of Zinc and Magnesium*, p. 2).

The formation of organomagnesium halides is a general reaction of the alkyl halides and of the monohalogen-substituted aromatic hydrocarbons such as bromobenzene, bromotoluenes, and bromonaphthalenes. Even under the most favourable conditions, with a rigid exclusion of all traces of moisture, the yield of the Grignard compound may fall short of the theoretical. Thus *tert.*-butylbromide gives only about 20—30% of the theoretical yield of *tert.*-butyl magnesium bromide, a considerable proportion of the alkyl bromide being evolved as butylene (Grignard, *Bull. Soc. chim.*, 1913, [iv], **13**, XI). *sec.*-Alkyl halides generally furnish better yields; but the best yields are obtained from primary alkyl halides. The following table records the average percentage yields of Grignard compound from different bromo-compounds under strictly comparable conditions (Gilman, Zoellner, and Dickey, *loc. cit.*; compare Gilman and McCracken, *J. Amer. Chem. Soc.*, 1923, **45**, 2462; R. Meyer and Tögel, *Annalen*, 1906, **347**, 55).

Ethyl	93	*tert.*-Amyl	24
n-Propyl	92	*n*-Hexyl	92
*iso*Propyl	84	*n*-Heptyl	89
n-Butyl	94	*n*-Octyl	88
*iso*Butyl	87	Bromobenzene	95
sec.-Butyl	78	*o*-Bromotoluene	93
tert.-Butyl	25	*m*-Bromotoluene	88
n-Amyl	89	*p*-Bromotoluene	87
*iso*Amyl	88	α-Bromonaphthalene	95
sec.-Amyl	67	β-Bromonaphthalene	84

A further source of loss is due to the reaction of the unchanged halide with the organo-metallic compound already formed.

$$R{\cdot}Hal + R{\cdot}Mg{\cdot}Hal \longrightarrow MgHal_2 + R{\cdot}R$$

This occurs to only a comparatively small extent with the majority of alkyl halides. Aryl iodides, however, give an appreciable quantity of diphenyl or its homologues, and the reaction occurs also to some extent with allyl bromide or iodide or with cinnamyl halides. These halides exhibit other abnormalities in their reaction with magnesium (compare Houben, *Ber.*, 1903, **36**, 2898).

Unsaturated halides of the type $R{\cdot}CH{:}CHBr$ can react with magnesium in ether, but the formation of the corresponding organomagnesium compound is accompanied by the production of unsaturated hydrocarbons owing to the elimination of hydrogen bromide. It is, however, possible to bring them into reaction with moderately good results for the purposes of syntheses by allowing magnesium to react with the unsaturated bromide in presence of a carbonyl compound (Krestinsky, *Ber.*, 1922, **55**, 2754, 2762, 2770; compare H. Davies and Kipping, *J.*, 1911, **99**, 296).

The preparation of Grignard reagents from dihalogen paraffins generally is not practicable. Those dihalogen paraffins with the halogens attached to adjacent carbon atoms yield olefins (see p. 369). Trimethylene bromide furnishes propylene (Zelinsky and Gutt, *Ber.*, 1907, **40**, 3049). The behaviour of the higher members of the series $BrCH_2(CH_2)_n{\cdot}CH_2Br$, where $n = 2, 3, 5$, or 8, has been examined by v. Braun and Sobecki (*Ber.*, 1911, **44**, 1918). They find that about half of the dibromide is converted into the normal organomagnesium halide,

$$BrMg{\cdot}CH_2(CH_2)_n{\cdot}CH_2MgBr,$$

the remainder being converted into a mixture of magnesium compounds represented by the general formula

$$BrMg{\cdot}CH_2{\cdot}(CH_2)_x{\cdot}CH_2{\cdot}MgBr.$$

(2) *Organo-Zinc Compounds.*—Reaction of alkyl iodides with zinc filings or with a zinc couple leads to the formation of alkyl zinc iodides, which are converted into zinc dialkyls on heating (E. Frankland, *J.*, 1850, **2**, 263; *Annalen*, 1849, **71**, 171; 1853, **85**, 346; 1855, **95**, 28; Ratke, *ibid.*, 1869, **152**, 220)

$$2CH_3I + 2Zn \longrightarrow 2ZnCH_3I \longrightarrow Zn(CH_3)_2 + ZnI_2$$

The preparation of zinc dialkyls by this method is now of little importance, since it has been largely superseded by the use of the Grignard reagents. The zinc alkyl halides, however, have an important application in the preparation of ketones from acyl chlorides (see p. 230). The following general method of preparing alkyl zinc iodides is given by Blaise (*Bull. Soc. chim.*, 1911, [iv], **9**, I).

Preparation of Zinc Alkyl Halides from Primary Alkyl Iodides.—One molecular proportion of the pure alkyl iodide diluted with about ⅓ * mol. proportion of pure dry ethyl acetate and an equal volume of toluene is mixed with twice the theoretical amount of zinc copper couple, and then heated at 100°. If the reagents are pure and dry, reaction soon starts—the addition of a little iodine usually initiates a sluggish reaction. The reaction proceeds regularly, and the mixture should be shaken from time to time. As the reaction slackens, the temperature is gradually raised to 110° and maintained at this till there is no further refluxing. The reaction is then complete. The mixture is diluted with a volume of toluene equal to that added initially. After cooling, the solution is decanted into a dry flask and the remaining zinc–copper couple washed with a little toluene. The solution thus prepared is then used for syntheses.

Secondary alkyl iodides react best with the zinc couple if the toluene is replaced by light petroleum (b. p. 85—90°). When the formation of the *sec.*-alkyl iodide is complete, an amount of benzene or toluene is added equal in volume to that of the light petroleum to completely dissolve the reagent.

This method of preparing zinc alkyl iodides does not give satisfactory results with *tert.*-alkyl iodides, nor can the aryl zinc iodides be prepared directly by this method.

For the preparation of these reagents only alkyl iodides can be used: the corresponding chlorides or bromides do not appear to react.

3. *Other Organo-metallic Compounds.*—Sodium alloys of some metals are able to react with alkyl iodides to form metal alkyl derivatives. Thus, sodium amalgam, when heated with ethyl iodide under suitable conditions, yields mercury diethyl (Frankland and Duppa, *J.*, 1863, **16**, 415). By using the appropriate sodium or potassium alloy, lead tetramethyl (Cahours, *Annalen*, 1862, **122**, 67); tin tetramethyl and tetraethyl (Ladenburg, *ibid.*, *Spl.* 1872, **8**, 64); bismuth triethyl (Breed, *ibid.*, 1852, **82**, 106); antimony triethyl (Löwig and Schweizer, *ibid.*, 1850, **75**, 315; Landolt, *J. pr. Chem.*, 1861, [i], **84**, 330), have been prepared. This method is no longer of any great practical value, for the majority of these metal alkyl derivatives can be more conveniently obtained by reaction of the appropriate Grignard reagent with the appropriate metal halide. It is however used to some extent for the preparation of some mercury organic compounds.

The reaction for the preparation of mercury organic compounds can be applied to the alkyl and aryl halides and is facilitated by the presence of ethyl acetate.

Preparation of Mercury Diphenyl.—Bromobenzene, mixed with an equal volume of benzene and a tenth of its weight of ethyl acetate, is added to an excess of 2·7% sodium amalgam. The mixture is heated under reflux in an oil-bath for 5 hours. More benzene is then added to dissolve any product which may have separated. The product is then filtered from sodium bromide. Removal of the solvent from the filtrate leaves mercury diphenyl, which is purified by crystallisation from benzene, m. p. 120° (Schlenk, Houben-Weyl, *Die Methoden der Organischen Chemie*, 1924, IV, p. 924; compare Aronheim, *Annalen*, 1878, **194**, 148; Dreher and Otto, *ibid.*, 1870, **154**, 94).

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* With alkyl iodides of comparatively high mol. wt. the amount of ethyl acetate should be increased to ½—¾ mol. proportion.

(b) *Reaction of Halogen Compounds with Organomagnesium Halides.*—The normal reaction of alkyl halides with the Grignard reagent is represented by the equation

$$RI + R'MgI \longrightarrow R{\cdot}R' + MgI_2$$

It is frequently found, however, that when an attempt is made to prepare hydrocarbons by this method, the product contains a large proportion of undesirable products such as unsaturated hydrocarbons, and hydrocarbons formed by the reduction of the radicles R and R′. The reaction is therefore of limited application only (Späth, *Monatsh.*, 1913, **34**, 1965). In general it appears that benzyl chloride reacts fairly smoothly with the lower alkylmagnesium halides yielding alkyl benzenes. The halogen of diphenyl- and triphenyl-methyl bromides is similarly replaced by alkyl in fairly good yield. This method has been used successfully for the preparation of Δ^{α}-olefins by allowing alkylmagnesium halides to act on allyl bromide (Brooks and Humphreys, *J. Amer. Chem. Soc.*, 1918, **40**, 833; R. Wilkinson, *J.*, 1931, 3057). The following general conditions are given by Wilkinson for the preparation of Δ^{α}-olefins from allyl bromide.

The Grignard reagent is prepared from the alkyl bromide and then forced over into a clean dry flask by means of a dry stream of nitrogen, precautions being taken to prevent access of moisture. The reagent is cooled by an external bath of cold water and stirred mechanically. Allyl bromide corresponding in amount to the magnesium in solution is now added slowly. The reaction is complete when the mixture becomes colourless. The stirring is continued thereafter for 30 minutes and the mixture gently warmed so that the ether refluxes. After keeping overnight, the ethereal solution is decanted from the magnesium bromide and distilled. If the olefin has a boiling point far removed from that of ether, a separation is effected by distillation through a fractionating column. If the boiling points are close together, the distillate is washed repeatedly with water till there is no further diminution in volume. It is then fractionated. The product contains some saturated hydrocarbons. The pure olefin is obtained by converting into dibromide and subsequently removing the halogen by treatment with zinc–copper couple in alcohol.

This type of reaction has also been used for the preparation of ethers by allowing the alkylmagnesium halide to react with halogen-substituted ethers. Thus monochloromethyl ether yields benzyl methyl ether by reaction with phenylmagnesium bromide (Reychler, *Bull. Soc. chim.*, 1907, [iv], **1**, 1198; Hamonet, *ibid.*, 1908, [iv], **3**, 254; compare Houben and Führer, *Ber.*, 1907, **40**, 4992).

(c) *Union of Radicles of Halogen Compounds under the Influence of*

Metals.—In this type of reaction, 2 molecules of the halide react in presence of a metal according to the equation.

$$2RI + 2Na \qquad R{\cdot}R + 2NaI.$$

The earliest record of such a condensation appears to be due to E. Frankland (*Annalen*, 1849, **71**, 171). He found that ethyl iodide, when heated at 130—140° in a sealed tube with the calculated amount of zinc, yielded a gas which was later recognised to be butane. Similarly methyl iodide gave ethane. Somewhat later, Wurtz (*Ann. chim.*, 1855, [iii], **44**, 275) found that sodium could take the place of zinc in this condensation, and used this method for the preparation of such hydrocarbons as octane, decane, heptane, and nonane. Furthermore, if a mixture of equimolecular proportions of two different alkyl halides were used, the product contained notable amounts of a hydrocarbon derived by the condensation of the dissimilar radicles $R{\cdot}R'$, as well as the hydrocarbons $R{\cdot}R$ and $R'{\cdot}R'$. The Wurtz reaction has been used fairly generally for the preparation of paraffin hydrocarbons. Thus *n*- and *iso*-hexanes have been prepared from *n*-propyl and *iso*propyl iodides; di*iso*butyl from *iso*butyl iodide (Schorlemmer, *Annalen*, 1867, **144**, 184; 1872, **161**, 277; Young and Fortey, *J.*, 1900, **77**, 1126). It has also been used to obtain the hydrocarbon $C_{60}H_{122}$ from myricyl iodide (Hell and Hägele, *Ber.*, 1889, **22**, 502).

The usual method of procedure consists in covering the necessary amount of sodium with dry ether and then adding the alkyl halide. Fractionation of the product when the reaction is complete yields the crude hydrocarbon, which is freed from unchanged alkyl halide by refluxing over sodium.

This reaction has the disadvantage that the yields are often poor and the product liable to contamination with unsaturated hydrocarbons and the product of the reduction of the alkyl halide. Thus *iso*propyl iodide is stated by Zander (*Annalen*, 1882, **214**, 167) to give about 5% of the theoretical yield of *iso*hexane, while *n*-propyl iodide furnishes *n*-hexane in 25% yield (compare Young and Fortey, *loc. cit.*). If special precautions are taken to free the sodium from all traces of oxide and rigorously to exclude moisture, better yields may be obtained (compare Faillebin, *Bull. Soc. chim.*, 1924, [iv], **35**, 160).

The Wurtz synthesis was extended by Tollens and Fittig (*Annalen*, 1864, **131**, 303) to the preparation of the alkyl benzenes by using a mixture of alkyl halide and aryl halide. The following general directions are given by Fittig and König (*Annalen*, 1867, **144**, 277; compare Fittig, Schaeffer, and König, *ibid.*, 1869, **149**, 324).

About 1½ times the theoretical amount of clean sodium in a round-bottomed flask fitted with an efficient reflux is covered with dry ether (about double the amount of mixed bromides). The mixture is cooled by an external bath of ice-water while a mixture of bromobenzene and alkyl bromide is slowly introduced. It is advantageous to use about 1¼ mol. proportions of alkyl bromide for 1 mol. proportion of aryl bromide. Reaction generally commences soon and is complete in a few hours. The ethereal solution is then decanted from the insoluble mixture of sodium and sodium bromide and fractionally distilled. The alkyl benzene is finally purified by refluxing over sodium.

This process has been used successfully with nuclear-substituted bromo-derivatives of homologues of benzene, and to a less extent with some dibromo-aromatic hydrocarbons. The yields of ethyl and propyl benzenes are fairly good, but for the preparation of the higher homologues this method is not uniformly satisfactory.

The union of aromatic radicles by treating the appropriate halogen compound with sodium does not proceed smoothly, and the yields are generally poor. Thus by the action of sodium on bromobenzene approximately only 5% of the theoretical amount of pure diphenyl can be obtained (Fittig, *Annalen*, 1862, **121**, 363; 1864, **132**, 201; Ullmann, *ibid.*, 1904, **332**, 40). Better results are obtained by using copper bronze as the condensing agent. This method is now generally used for the preparation of derivatives of diphenyl from halogen-substituted derivatives of benzene.

Preparation of Diphenyl.—Iodobenzene (20 g.) and copper bronze (20 g.) are heated in a sealed tube for 3 hours at 230°. Extraction of the product with ether and subsequent evaporation of the solvent yields a reddish oil which solidifies and after distillation furnishes diphenyl—yield 9 g.

Alkyl derivatives of diphenyl are similarly prepared by using halogen-substituted homologues of benzene. β-Iodonaphthalene furnishes 22′-dinaphthyl (Ullmann, *Annalen*, 1904, **332**, 40).

Preparation of 2 : 2′-Dinitrodiphenyl.—*o*-Bromonitrobenzene (5 g.) is heated in a test-tube at 200°, and while stirring with a thermometer, 3 g. of copper bronze are gradually added. The copper loses its lustre and the mass becomes viscous. The reaction is completed by warming at 210—220° for a short time. After cooling somewhat, the mass is extracted with benzene. 2 : 2′-Dinitrodiphenyl is obtained by concentrating the extract—yield 76% of theoretical (Ullmann and Bielecki, *Ber.*, 1901, **34**, 2176).

Preparation of the Methyl Ester of 6 : 6′-Dinitrodiphenic Acid.—Copper bronze (10 g.) is added gradually to the methyl ester of 2-chloro-3-nitrobenzoic acid, maintained at 210°. The reaction is completed by heating the mixture at 225—235° for 1 hour. Extraction of the cooled mass with benzene removes the ester of the dinitrodiphenic acid. It separates from benzene as pale yellow crystals, m. p. 132—133°—yield 5 g. (Kenner and Stubbings, *J.*, 1921, **119**, 598). Other derivatives of diphenylcarboxylic acids are prepared similarly (compare Christie, James, and Kenner, *J.*, 1923, **123**, 1949).

Preparation of 4 : 4′-Diphenyldiphenyl, $Ph{\cdot}C_6H_4{\cdot}C_6H_4{\cdot}Ph$.—A mixture of 2 g. of 4-iododiphenyl and 2 g. of copper bronze is heated. At about 220° reaction commences, and the temperature is gradually raised to 270°. At this point heat is evolved and the temperature of the mixture rises spontaneously to 285°. When the vigour of the reaction subsides, the mixture is kept at 265—270° for 10 minutes. It is cooled, powdered, and then heated under a pressure of about 15 mm. A small amount of unchanged 4-iododiphenyl sublimes at about 150°. 4 : 4′-Diphenyldiphenyl is obtained as a white crystalline sublimate at 330°. It is purified by crystallisation from nitrobenzene—m. p. 320° (Bowden, *J.*, 1931, 1113; compare Ullmann, *Annalen*, 1904, **332**, 51).

This type of condensation has also been used for the preparation of diphenyl aldehydes from halogen-substituted benzaldehydes, the

–CHO group being protected by conversion into an azomethine before heating with copper bronze. Acyl derivatives of halogen-substituted amines condense normally. Chloro-substituted diphenyls have also been obtained by this reaction by condensing chloro-iodobenzenes in presence of copper bronze (Ullmann, *loc. cit.*).

Silver powder has also been used for the condensation of halogen compounds, but has received only a limited application. By its use, polyphenyls, such as 1 : 4-di-diphenylbenzene, have been prepared (Gerngross and Dunkel, *Ber.*, 1924, **57**, 746; Pummerer and Bittner, *ibid.*, 1931, **64**, 2477). It is, however, less efficient than copper bronze, and the reaction is often not a smooth one. Silver powder is also used for the formation of esters of dibasic acids from the esters of monohalogen-substituted fatty acids. Thus finely-divided silver converts the ester of β-iodopropionic acid into adipic ester (J. Wislicenus, *Annalen*, 1869, **149**, 220; D. B. Jones, *J. Amer. Chem. Soc.*, 1915, **37**, 586; Hell and Rothberg, *Ber.*, 1888, **22**, 60; Hell and W. Mayer, *ibid.*, p. 48).

An elegant method for this preparation of diphenyl from bromobenzene has been described by Krizewsky and E. E. Turner (*J.*, 1919, **115**, 559). It has since been applied by Bowden (*loc. cit.*) to the preparation of 4 : 4′-diphenyldiphenyl. The following description illustrates the method.

Preparation of Diphenyl.—Anhydrous cupric chloride (28 g.) and bromobenzene (32 g.) are added to magnesium turnings (4·9 g.) covered by 150 c.c. of dry ether. The mixture is shaken at frequent intervals and the vigour of the reaction moderated when necessary by external cooling. The mixture is finally heated under reflux for 2 hours and then ice-water and diluted hydrochloric acid are added. The ether is separated and the aqueous layer extracted several times with ether. The combined ethereal solutions are washed with water to remove the last traces of copper chloride, dried, and evaporated. Diphenyl remains, m.p. 70°—yield 13 g. (Krizewsky and Turner, *loc. cit.*).

(6) *Reaction of Halogen Compounds with Metal Salts.*

When an alkyl halide reacts with salts of acids, there is, in general, a more or less complete replacement of the metal by the alkyl group. Thus alkyl cyanides are formed with potassium cyanide; potassium or silver acetates yield esters; silver nitrite gives a mixture of alkyl nitrite and nitro-paraffin. In the succeeding paragraphs only the more important of these reactions will be dealt with.

(a) *Metal Halides.*—There are many examples recorded in the literature of the more or less complete replacement of one halogen by another when an alkyl halide or some other halogen compound is treated with a metal halide. Thus ethyl or propyl fluorides are obtained by reaction of the appropriate alkyl iodides with silver fluoride at room temperature. With silver fluoride the alkyl bromides and chlorides react less readily, and require to be heated in sealed tubes before complete replacement is effected.

The replacement of chlorine and bromine by iodine is of importance. It has been effected by heating with calcium iodide in sealed tubes (v. Romburgh, *Rec. trav. chim.*, 1883, **1**, 151; Spindler, *Annalen*, 1885, **231**, 257); more conveniently by the action of potassium iodide in methyl alcohol (W. H. Perkin, sen., and Duppa, *Annalen*, 1859, **112**, 125). An elegant and simple method of effecting this change, due to Finkelstein (*Ber.*, 1910, **43**, 1528), consists in treating the halogen compound with a solution of sodium iodide in acetone. It is well suited for the preparation of most alkyl iodides, α-iodo-ketones, and iodo-substituted fatty acids, benzyl iodide, and its substitution products. It fails, of course, if the halogen is unreactive, as in the aryl halides. It cannot be used for the preparation of di-iodo-compounds containing the halogens united to adjacent carbon atoms, since these compounds readily lose iodine to form unsaturated compounds.

Preparation of iso*Amyl Iodide.*—*iso*Amyl bromide (15 g.) is boiled for 1 hour with a 15% solution of sodium iodide in acetone. About one-third of the acetone is then distilled off and the residue poured into water. The oil thus obtained is separated, shaken with mercury to remove free iodine, and after drying, distilled under reduced pressure.

Although a similar process can be applied to many other alkyl bromides, *tert.*-butyl bromide reacts very slowly under these conditions. The method is therefore not recommended for the preparation of *tert.*-butyl iodide.

Preparation of p-*Nitrobenzyl Iodide.*—10 C.c. of *N*-sodium iodide are added to a solution of 1·7 g. of *p*-nitrobenzyl chloride in acetone. Sodium chloride separates rapidly, and is collected by filtration. The filtrate deposits *p*-nitrobenzyl iodide as long needles, m. p. 124°—yield 2·6 g.

(b) *Metal Cyanides.*—Reaction between alkyl halides and metal cyanides takes place to furnish either cyanides (b) or *iso*cyanides (a):

$$\mathrm{RI} + \mathrm{MCN}\begin{array}{l}\nearrow \mathrm{R{\cdot}N}\vdots\mathrm{C}\quad (a)\\ \searrow \mathrm{R{\cdot}C}\vdots\mathrm{N}\quad (b)\end{array}\qquad \mathrm{M} = \text{any metal radicle.}$$

The relative proportions of the two products appear to depend largely on the metal cyanide used. *iso*Cyanide is the principal product of the action of the lower alkyl halides on silver cyanide. It is obtained as a double compound with silver cyanide, from which it is isolated by the addition of a concentrated solution of potassium cyanide. Mercuric and zinc cyanides also yield a high proportion of *iso*cyanide by reaction with alkyl iodide (Gautier, *Compt. rend.*, 1868, **65**, 468, 862; *Bull. Soc. chim.*, 1869, [ii], **11**, 214; Calmels, *Compt. rend.*, 1884, **99**, 239; compare Guillemard, *Ann. chim.*, 1908, [viii], **14**, 311).

The alkali cyanides give nitriles as the principal product of the interaction with alkyl halides. This method is largely used for the preparation of simple nitriles.

Preparation of Benzyl Cyanide.—A mixture of powdered sodium cyanide (52 g.) and water (45 c.c.) is warmed in a flask fitted with a reflux condenser. When all the salt has dissolved, benzyl chloride (103 g.) diluted with an equal volume of alcohol is added slowly. The reaction is completed by heating in a water-bath for 2—3 hours. The sodium chloride which has separated is removed by filtration and washed with a small amount of alcohol. As much as possible of the alcohol in the filtrate is distilled off from a water-bath and the benzyl cyanide in the residue separated from the aqueous layer.

The resultant crude benzyl cyanide is distilled under reduced pressure —yield of pure product 75—85 g.—b. p. 115—120°/10 mm. (Adams and Thal, *Organic Syntheses*, 1922, **2**, 9).

Although the halogen of aryl halides is comparatively inert, Rosenmund and Struck (*Ber.*, 1919, **52**, 1749) find that interaction with potassium cyanide can be achieved by heating the aryl halide at 200° with an aqueous alcoholic solution of potassium cyanide to which has been added some cuprous cyanide. Under these conditions hydrolysis of the cyano-group occurs, with the result that the halogen is replaced by a carboxyl group. Thus bromobenzene yields benzoic acid; *p*-bromoanisole furnishes anisic acid.

(c) *Salts of Carboxylic Acids.*—Reaction between alkyl halides and salts of carboxylic acids results in the formation of esters:

$$RI + NaO_2C{\cdot}R' \longrightarrow RO_2C{\cdot}R' + NaI$$

Some of the applications of this reaction have already been referred to (p. 201). When direct methods of introducing the hydroxyl are unsatisfactory, it is frequently possible by its use to replace halogen by hydroxyl by the hydrolysis of the resultant ester.

The general procedure is to allow the halogen compound to react with the silver salt of the appropriate acid, or more generally to heat the halogen compound with the potassium salt in a solution of the corresponding acid. Primary alkyl halides react normally; secondary halides furnish a poorer yield of ester owing to their greater tendency to eliminate halogen hydride; *tert.*-alkyl halides, however, yield olefin as the principal product. These generalisations also apply to di- and tri-halogen-substituted paraffins. Thus while ethylene dibromide and trimethylene dibromide furnish the corresponding esters in good yield, βγ-dibromobutane and propylene dibromide furnish a mixture of the ester and unsaturated bromo-olefin (Bainbridge, *J.*, 1914, **105**, 2291; Mereschkowsky, *Annalen*, 1923, **431**, 231).

The following general conditions for effecting the conversion of bromo-compounds into esters are given by Mereschkowsky (*loc. cit.*).

The bromo-compound is boiled under reflux with finely-powdered and freshly fused potassium acetate (1½ mol. proportions, for every atomic proportion of bromine) and as many c.c. of glacial acetic acid as there are grams of potassium acetate.

The duration of the reaction depends on the position of the bromine in the compound. The end of the reaction can usually be recognised by the solution becoming clear and that no more potassium bromide separates.

The solution is then diluted with water and the ester taken up in ether.

Preparation of Glycol Diacetate.—Ethylene dibromide (75 g.), glacial acetic acid (25 g.), and finely-powdered dry potassium acetate (75 g.) in a ½-litre distillation flask fitted with a reflux condenser and tilted so that the side tube of the flask is inclined upward, are heated vigorously on a wire gauze so that it refluxes briskly. After about 2 hours, the reflux condenser is removed, and after attaching it to the side arm of the distillation flask, the flask is tilted for ordinary distillation and the reaction product is distilled over by heating with a luminous flame.

The distillate is mixed with a further 75 g. of ethylene dibromide and 90 g. of potassium acetate and again heated under reflux for 2—3 hours.

The reaction product is again distilled over, and then fractionally distilled through a short fractionating column. After two or three fractionations most of the glycol diacetate is concentrated in the distillate collected between 180° and 190°.

Treatment of the lower-boiling fractions with potassium acetate as described above gives a further amount of the diacetate.

Preparation of Benzyl Acetate.—Benzyl chloride (150 g.), potassium acetate (110 g.), and 200 g. of glacial acetic acid are heated under reflux for 20 hours. The bulk of the acetic acid is then distilled off till the vapour has a temperature of 120°. The residue is then treated with water. The benzyl acetate which separates is washed with water, dried, and distilled, b. p. 206°—yield 75—80% of theory (Seelig, *J. pr. Chem.*, 1889, [ii], **39**, 164).

(d) *Metal Nitrites.*—Interaction of alkyl halides with dry silver nitrite results in the formation of a mixture of alkyl nitrite and the isomeric nitro-compound (V. Meyer, *Annalen*, 1874, **171**, 1).

$$R\cdot CH_2\cdot I + AgNO_2 \begin{array}{l} \nearrow R\cdot CH_2\cdot ONO + AgI \\ \searrow R\cdot CH_2\cdot NO_2 + AgI \end{array}$$

The relative proportions of the two products depends partly on the type of alkyl halide. The halogen also has its influence. This is evident from the measurements of Reynolds and Adkins (*J. Amer. Chem. Soc.*, 1929, **51**, 279). With the lower alkyl halides it appears that, with few exceptions, larger yields and larger proportions of nitro-paraffin in the product are obtained from alkyl bromides than from the corresponding chlorides and iodides. The proportion of nitro-paraffin in the product does not appear to be seriously influenced by the length of the carbon chain. Primary alkyl halides in general give higher yields of nitro-compounds than *iso-*, *sec-*, or *tert.*-alkyl halides.

The replacement of the halogen does not always proceed smoothly, for some iodides such as *tert.*-butyl or *cyclo*hexyl iodides give poor yields either of nitro-compound or nitrite, owing to the occurrence of side reactions (compare Kohler, *J. Amer. Chem. Soc.*, 1916, **38**, 898).

The reaction has been extended to the preparation of nitro-derivatives from benzyl halides, of dinitro-compounds from dihalogen paraffins such as trimethylene di-iodide (Keppler and V. Meyer, *Ber.*, 1892, **25**, 1709), 1 : 4-di-iodobutane, 1 : 5-di-iodopentane, 1 : 10-di-iododecane (v. Braun and Sobecki, *Ber.*, 1911, **44**, 2528).

Preparation of p-*Nitrophenyl Nitromethane.*—A moderate excess of dry silver nitrite is added to *p*-nitrobenzyl iodide in a mixture of ether and benzene so proportioned as to boil at about 50°. The mixture is kept for 12 hours at room temperature, and after grinding up the precipitate, heated under reflux for 2 hours. It is then filtered and the filtrate shaken with aqueous alkali.

The *iso*nitroso-compound is precipitated from the ice-cold alkaline solution by the addition of dilute acid. It is collected and crystallised from alcohol, m. p. 91° (Hantzsch and Veit, *Ber.*, 1899, **32**, 621).

Preparation of Phenylnitromethane.—Silver nitrite (17 g.) is added to benzyl chloride (12 g.) cooled in a bath of ice-water. After keeping for 24 hours, the product is extracted with ether. The extract is dried over calcium chloride and then evaporated. The residue is treated with an equal weight of a 4% solution of sodium in methyl alcohol, when the sodium salt of the *iso*nitroso-compound is precipitated. It is collected by filtration and thoroughly drained by pressing it on the funnel. It is then dissolved in water, the calculated amount of acetic acid added, and the liberated nitro-compound extracted by ether.

After drying the ethereal extract, phenylnitromethane is obtained as an oil by evaporating the ether (Hollemann, *Rec. trav. chim.*, 1894, **13**, 405).

Preparation of β-Nitropropane.—Finely-powdered silver nitrite (100 g.) is added—a little at a time—to 100 g. of *iso*propyl iodide dissolved in 300 c.c. of dry ether. The reaction is allowed to proceed without any cooling, and is not shaken till the temperature of the reaction mixture begins to fall. It is then shaken vigorously and boiled under reflux for 12 hours. The precipitate is filtered and extracted several times with ether. The combined extracts and filtrate are then distilled.

β-Nitropropane is collected at 120°—yield 12—15 g. (Kohler, *J. Amer. Chem. Soc.*, 1916, **38**, 898).

(e) *Reaction with Metal Derivatives of Malonic Esters, β-Keto Esters, and β-Diketones.*—Alkali metal derivatives of acetoacetic ester and similar β-keto esters, β-diketones, and esters of malonic acid react with suitable halogen compounds to replace the metal by the alkyl group. This reaction is usually effected in alcoholic solution, but it may also be effected by treating a suspension of the appropriate sodio compound in an indifferent solvent with a suitable alkyl halide.

This reaction, in so far as it concerns β-ketonic esters and malonic esters, is of considerable importance for synthetic purposes (see pp. 103, 104, 205).

Preparation of Ethylmalonic Ester (Method 1).—A solution of 2·3 g. of sodium in 25 g. of absolute alcohol is mixed with 16 g. of malonic ester and 20 g. of ethyl iodide. In a short time there is a precipitate and the liquid commences to boil. The mixture is then refluxed till it is neutral to moist litmus paper. The greater part of the alcohol is distilled off on the water-bath, the residue treated with water, and the ester taken up in ether. After washing the ethereal solution with water and drying over calcium chloride, the solvent is evaporated and the ester distilled. Ethylmalonic ester is collected at 206—208° (Conrad, *Annalen*, 1880, **204**, 134).

(Method 2).—Malonic ester (100 g.) is added to 14·4 g. of sodium wire covered by 300 c.c. of dry ether. The mixture is shaken vigorously from time to time, and finally heated under reflux till the last trace of sodium has reacted. After cooling ethyl iodide (100 g.) is added. Reaction begins immediately and is completed by heating on the water-bath till the mixture is neutral to moist litmus paper. The greater part of the ether is then distilled off, water added, and the ester separated. It is washed with dilute sodium carbonate solution and water, dried over calcium chloride, and distilled. The crude ethyl malonic ester passes over at 209—215°—yield 102 g. The product contains some diethyl malonic ester (Michael, *J. pr. Chem.* ,1905, [ii], **72**, 548).

Preparation of n-*Butyl Malonic Ester.*—A solution of sodium ethoxide in ethyl alcohol is prepared by dissolving 23 g. of sodium in 500 g. of absolute alcohol. When the freshly prepared solution has cooled to about 50°, diethylmalonate (164 g.) is gradually added, and then 137 g. of butyl bromide, which should be added slowly. The reaction mixture is heated under reflux till it is neutral to moist litmus paper. As much as possible of the alcohol is then distilled off from a water-bath, and the residue diluted with about 400 c.c. of water. The mixture is thoroughly shaken. *n*-Butyl malonic ester separates as an oil, which is removed and distilled under reduced pressure. The pure ester is collected at 130—135°/20 mm.—yield 170—195 g. (Adams and Kamm, *Organic Syntheses*, 1925, **4**, 11).

The introduction of a second alkyl group can be effected by treating the monoalkyl derivative with sodium ethoxide and the appropriate alkyl halide exactly as described for the preparation of the monoalkyl derivatives. In this way dissimilar alkyl groups can be introduced. The preparation of dialkyl-substituted malonic esters with similar alkyl groups can be effected in one operation, by adding the necessary amount of alcoholic sodium alkoxide and alkyl halide.

Preparation of Diethyl Malonic Ester.—Malonic ester (32 g.) is added to a freshly prepared solution of 9·2 g. of sodium in 150 c.c. of absolute alcohol. Ethyl iodide (80 g.) is then added, and when the reaction which sets in has subsided, the mixture is heated under reflux till it is neutral to moist litmus paper. The subsequent treatment is similar to that employed for the isolation of other alkyl malonic esters described above—yield 30 g. of diethyl malonic ester, b. p. 223°.

The introduction of alkyl groups into acetoacetic ester is generally accomplished under the following conditions.

Acetoacetic ester diluted with its own volume of dry ether or benzene is treated with slightly less than the theoretical amount of sodium or granulated sodium (1 mol.). When the formation of the sodio-compound is complete—it may be necessary to warm the mixture to complete the reaction—the appropriate halogen compound is added. After the initial reaction has subsided, the mixture is heated under reflux till it is neutral to moist litmus paper. Water is then added, the upper layer of the substituted acetoacetic ester separated, washed with water, and dried over anhydrous magnesium sulphate. Fractional distillation under reduced pressure yields the pure product.

By a similar treatment of the mono-substituted acetoacetic ester a second group can be introduced.

A large variety of groups may be introduced by this procedure—such as alkyl, benzyl, allyl, fatty acid ester residues, and hydroxy-alkyl groups (J. Wislicenus, *Annalen*, 1877, **186**, 216).

A similar procedure can be applied to many other β-keto-esters.

Preparation of αα-Dimethylbenzoyl Acetic Ester.—α-Methylbenzoyl acetic ester (15 g.) is added to granulated sodium (1·8 g.) in toluene and the mixture kept at room temperature for about 3 hours, when the formation of the sodio-compound is complete. The resulting solution is decanted from traces of unchanged sodium and mixed with methyl iodide (11 g.). After heating under reflux for about 3 hours, the mixture is diluted with ether and then treated with water. The ether-toluene layer is washed first with dilute hydrochloric acid and then with water and dried. After removal of the solvents, the residue is distilled under reduced pressure, b. p. 153—156°/19 mm.—yield 60—70% of theory (Hope and W. H. Perkin, jun., *J.*, 1909, **95**, 2046).

The preparation of the simple alkyl derivatives of acetoacetic ester can be accomplished by the action of the appropriate alkyl halide on an alcoholic solution of the acetoacetic ester containing the necessary amount of sodium ethoxide (see p. 103).

7. *Special Reactions of Halogen Compounds.*

(a) *Formation of Additive Compounds of Iodo-compounds and their Reactions.*—Iodobenzene combines additively with chlorine to yield phenyl iodochloride, $Ph{\cdot}ICl_2$. Iodochlorides of alkyl, bromo-, chloro-, and nitro-substituted benzenes are similarly derived, as also are the iodo-chlorides of naphthalene. The presence of several negative groups in the aromatic nucleus appears to prevent the addition of chlorine to the iodo-group, for no iodochloride has been isolated from penta- and tetra-chloro-iodobenzenes. Combination of the iodo-compound with chlorine is generally effected by passing chlorine into the appropriate iodo-compound diluted with chloroform. Glacial acetic acid or light petroleum can also be used as solvents (Willgerodt, *Ber.*, 1893, **26**, 1533, 1947; 1896, **29**, 1568; *J. pr. Chem.*, 1905, [ii], **71**, 540; Willgerodt and Böllert, *Ber.*, 1910, **43**, 2641; Willgerodt and Wilcke, *ibid.*, p. 2746).

Preparation of Phenyl Iodochloride.—A solution of 5 g. of iodobenzene in 20 c.c. of chloroform is cooled in ice and dry chlorine passed in till no more chlorine is taken up. The solution sets to a paste of light yellow needles, which are filtered under suction and dried on porous earthenware (Willgerodt, *J. pr. Chem.*, 1886, [ii], **33**, 155).

Some aliphatic compounds also yield iodochlorides. Thus methyl and ethyl iodides furnish unstable iodochlorides by adding the necessary amount of chlorine dissolved in carbon tetrachloride to a solution of the alkyl iodide in light petroleum cooled by a mixture of ether and solid carbon dioxide. Diodoethylene, $CHI{:}CHI$, and chloroiodoethylene, $CHI{:}CHCl$, form more stable iodochlorides (Thiele and Haackh, *Annalen,* 1909, **369**, 135; Thiele and Peter, *ibid.*, p. 149).

The iodochlorides liberate iodine from potassium iodide and are reduced by alcohol. Treatment with aqueous alkali converts them into iodoso-compounds.

$$Ph{\cdot}ICl_2 + 2NaOH \longrightarrow Ph{\cdot}IO + 2NaCl + H_2O$$

It is sometimes advisable to use aqueous sodium carbonate or bicarbonate instead of alkali hydroxide. This applies particularly to the preparation of iodoso-compounds from iodoethylene iodochloride, from chloroethylene iodochloride, and from polyhalogen-substituted phenyl iodochlorides (Thiele, *loc. cit.*; Willgerodt and Wilcke, *loc. cit.*). Iodoso-compounds also result by the gradual addition of water to a pyridine solution of the aryl iodochloride (Ortoleva, *Z.*, 1900, **1**, 722).

Preparation of Iodosobenzene (Method 1).—Phenyl iodochloride (3 g.) is ground up with 15 c.c. of 10% aqueous sodium hydroxide in a mortar. After keeping overnight, the iodosobenzene is collected by filtration, washed with water, and dried on porous earthenware.

(Method 2.)—A solution of 1 g. of phenyl iodochloride in 3 c.c. of pyridine is diluted by the gradual addition of 50 c.c. of water. An oil separates, which soon solidifies to an amorphous mass. It is collected and washed successively with water, ether, and chloroform.

Iodoso-compounds liberate iodine from potassium iodide; they behave in general as the anhydrides of the hypothetical diacid base $R{\cdot}I(OH)_2$. By dissolving an iodoso-compound in glacial acetic acid and subsequent crystallisation of the solution, the diacetate $R{\cdot}I(O_2C{\cdot}CH_3)_2$ is obtained. Diformates and dipropionates have also been prepared as well as dinitrates, chromates, basic sulphates, and basic nitrates. The nitrate is prepared by treating the iodoso-compound with dilute nitric acid; the chromate by the addition of chromium trioxide to an acetic acid solution of the iodoso-compound. Iodochlorides are none other than the chlorides of iodoso-compounds. Basic salts are generally obtained from aryl iodoso-compounds containing several negative substituents in the nucleus (Willgerodt, *Ber.*, 1893, **26**, 1309; Willgerodt and Wilcke, *loc. cit.*).

Under suitable conditions, iodoso-compounds are oxidised to iodoxy-compounds, $R{\cdot}IO_2$. With iodosobenzene this occurs by heating at 90—100° (Willgerodt, *Ber.*, 1892, **25**, 3500), or more conveniently by boiling with water. This latter method has been applied to the preparation of a number of homologues of iodoxybenzene.

$$2Ph{\cdot}IO \longrightarrow Ph{\cdot}I + Ph{\cdot}IO_2$$

Preparation of p-*Iodoxytoluene.*—*p*-Iodosotoluene is boiled with water. It gradually dissolves, and *p*-iodotoluene distils over in steam. Iodoxytoluene is deposited as a white crystalline solid on cooling the non-volatile aqueous residue. It decomposes at 228° on heating in a capillary tube (Willgerodt, *Ber.*, 1893, **26**, 360).

Oxidation of this kind is often effected very conveniently by means of aqueous hypochlorite. Iodoxy-compounds have been prepared also by the direct oxidation of iodobenzene and its homologues by means of permonosulphuric acid, while many iodo-compounds are oxidised by peracetic or perbenzoic acids to iodoso- or to iodoxy-compounds. In the case of aliphatic compounds the iodo-group must be attached to a doubly-bound carbon atom for this type of oxidation to occur. Thus iodofumaric acid is oxidised to iodosofumaric acid (Böeseken and Schneider, *Proc. K. Akad. Wetensch. Amsterdam,* 1930, **33**, 827; 1932, **35**, 1140).

Iodoxy-compounds appear to have no basic properties. They react with iodoso-compounds in aqueous suspension, preferably in presence of moist silver oxide, to yield iodinium compounds. Thus an intimate mixture of iodoso- and iodoxy-benzenes shaken with a suspension of silver oxide in water yields a filtrate which is strongly alkaline owing to the formation of diphenyliodinium hydroxide, $Ph_2{\cdot}IOH$. The addition of potassium iodide, preferably after reducing the iodate present by sulphurous acid, precipitates diphenyliodinium iodide, $Ph_2{\cdot}II$. This reaction can be fairly generally applied to the preparation of nitro-, halogen-, and alkyl-substituted aryliodoso- and iodoxy-compounds.

$$Ph{\cdot}IO + Ph{\cdot}IO_2 + H_2O \longrightarrow Ph_2I(OH) + HIO_3$$

This interaction occurs to some extent during the preparation of iodoxy-compounds by boiling iodoso-compounds with water. The iodinium iodide can be obtained in this way by adding potassium iodide to the aqueous mother-liquor obtained after the separation of the iodoxy-compound (Hartmann and V. Meyer, *Ber.*, 1894, **27**, 504, 1598).

Some unsymmetrical substituted iodoaryl-iodinium salts are obtained directly from iodosobenzene and some of its homologues by treatment with concentrated sulphuric acid.

$$2PhIO + H_2SO_4 \qquad (IC_6H_4{\cdot}I{\cdot}Ph)HSO_4 + H_2O$$

(Hartmann and V. Meyer, *Ber.*, 1894, **27**, 427; Willgerodt and Howells, *ibid.*, 1900, **33**, 847; Willgerodt and Schmierer, *ibid.*, 1905, **38**, 1477).

(b) *Isomerisation of Halogen Compounds.*—*iso*Butyl bromide is converted into *tert.*-butyl bromide on heating. The reverse change of the *tert.*-bromide to *iso*butyl bromide also occurs under similar conditions, an equilibrium being attained when the mixture contains about 80% of *tert.*-butyl bromide (Eltckoff, *Ber.*, 1873, **6**, 1258; 1875, **8**, 1244; Faworsky, *Annalen*, 1907, **354**, 325; Michael and Leupold, *ibid.*, 1911, **379**, 263). This reaction has since been studied in some detail (Michael and Zeidler, *Annalen*, 1912, **393**, 81; Michael, Scharf, and Voigt, *J. Amer. Chem. Soc.*, 1916, **38**, 653; Brunel, *ibid.*, 1917, **39**, 1978; *Annalen*, 1911, **384**, 245). Pure *iso*butyl bromide is comparatively easily isomerised. In the vapour phase some specimens are transformed into the *tert.*-bromide to the extent of 2·7% after 3 hours at 100°; 54% after ½ hour at 184°. In the liquid phase a transformation of 82% has been observed after 3 hours at 142°. The rate of isomerisation is dependent very largely on the presence of impurities. *iso*- and *tert.*-Butyl alcohols or di*iso*butene which are normal impurities in most specimens of *iso*butyl bromide retard the change. The type of glass used for the enclosing vessels also has an important effect. A trace of zinc bromide is sufficient to catalyse the isomerisation very markedly (Michael, Scharf, and Voigt, *loc. cit.*).

Other bromides which have been shown to isomerise on heating are *iso*- and *n*-propyl bromides; *iso*- and *tert.*-amyl bromides. These changes have been effected by passing the vaporised halides over barium chloride or thorium chloride at 250° and then over pumice at 200°. The yields of *tert.*-amyl and *tert.*-butyl bromides from the corresponding *iso*bromides are about 60—75%; *n*-propyl bromide gives *iso*propyl bromide in 25% yield (Sabatier and Mailhe, *Compt. rend.*, 1913, **156**, 659).

A similar rearrangement takes place at room temperature under the influence of aluminium chloride (Gustavson, *Ber.*, 1883, **16**, 958), and this no doubt is responsible for the production of *tert.*- and *sec.*-alkyl benzenes in the Friedel–Crafts reaction when primary alkyl derivatives might have been expected (see p. 46).

Changes of this type do not appear to be confined to the alkyl halides. Faworsky (*loc. cit.*) has shown that some dibromides such as ethylene dibromide, propylene dibromide, and the butylene dibromides undergo isomerisation on heating in sealed tubes at between 200° and 300°.

TABLE XXIII.

Halogen Compounds.

	B. p.	M. p.	*d.*	
Methyl chloride	—24°	—	—	
Methyl bromide	4·5	—	—	MeHgBr (*a*), m. p. 160°.
Ethyl chloride	13	—	$0{\cdot}917^{6}_{6}$	
Vinyl bromide	16	—	—	Polymerises readily to rubber-like mass.
*iso*Propyl chloride	37	—	$0{\cdot}859^{20}$	Anilide (*b*), m. p. 103°.
Ethyl bromide	38	—	$1{\cdot}4555^{20}_{4}$	EtHgBr (*a*), m. p. 194°.
Methylene dichloride	42	—	$1{\cdot}336^{20}_{4}$	
Methyl iodide	42	—	$2{\cdot}279^{20}_{4}$	MeHgI (*a*), m. p. 145°; *a*-naphthalide (*c*), m. p. 161°; 3 : 5-dinitrobenzoate (*d*), m. p. 110°.
n-Propyl chloride	46	—	$0{\cdot}891^{20}_{4}$	Anilide (*b*), m. p. 92°; *a*-naphthalide (*c*), m. p. 121°.
Allyl chloride	46	—	$0{\cdot}938^{20}_{4}$	
tert.-Butyl chloride	52	—	—	Hydrolysed by hot water to *tert.*-butyl alcohol.
Ethylidene dichloride	57	—	$1{\cdot}175^{20}_{4}$	
*iso*Propyl bromide	59	—	$1{\cdot}310^{20}_{4}$	*β*PrHgBr (*a*), m. p. 94°; anilide, m. p. 103°.
Chloroform	61	—	$1{\cdot}504^{12{\cdot}5}_{4}$	Prolonged action of alcoholic potash yields KCl and K_2CO_3. *iso*Nitrile reaction.
sec.-Butyl chloride	67	—	$0{\cdot}871^{26}_{4}$	
*iso*Butyl chloride	69	—	—	
2 : 2-Dichloropropane	70	—	$1{\cdot}093^{20}_{20}$	
n-Propyl bromide	71	—	$1{\cdot}354^{20}_{4}$	PrHgBr (*a*), m. p. 138°.
Allyl bromide	70	—	$1{\cdot}398^{20}_{4}$	Anilide (*b*), m. p. 114°.
tert.-Butyl bromide	73	—	$1{\cdot}211^{20}_{4}$	
Ethyl iodide	72	—	$1{\cdot}946^{12}_{4}$	EtHgI (*a*), m. p. 182°; *a*-naphthalide (*c*), m. p. 126°.
Carbon tetrachloride	77	—	$1{\cdot}595^{20}_{4}$	
n-Butyl chloride	78	—	$0{\cdot}884^{20}_{4}$	Anilide (*b*), m. p. 63°; *a*-naphthalide (*c*), m. p. 112°.
tert.-Amyl chloride	86	—	$0{\cdot}871^{15}_{4}$	
Ethylene dichloride	84	—	$1{\cdot}258^{17{\cdot}2}_{4}$	
*iso*Propyl iodide	88	—	$1{\cdot}703^{20}_{4}$	Anilide (*b*), m. p. 103°.
sec.-Butyl bromide	90	—	$1{\cdot}251^{25}_{4}$	
Trichloroethylene	88	—	$1{\cdot}465^{20}_{4}$	
*iso*Butyl bromide	92	—	$1{\cdot}259^{25}_{4}$	*iso*BuHgBr (*a*), m. p. 56°.
2-Bromo-Δ^2-butene	94	—	$1{\cdot}321^{26}_{4}$	
Methylene dibromide	98	—	$2{\cdot}499^{15}_{15}$	
n-Butyl bromide	100	—	$1{\cdot}275^{20}_{4}$	BuHgBr (*a*), m. p. 129°; anilide (*b*), m. p. 63°; *a*-naphthalide (*c*), m. p. 112°.
tert.-Butyl iodide	100	—	$1{\cdot}370^{18{\cdot}5}_{15}$	Warm water yields *tert.*-butyl alcohol. Alkali yields butylene.
n-Propyl iodide	102	—	$1{\cdot}743^{20}_{4}$	Anilide (*b*), m. p. 92°; *a*-naphthalide (*c*), m. p. 121°.
*iso*Amyl chloride	100	—	—	
Allyl iodide	102	—	$1{\cdot}889^{18{\cdot}5}_{4}$	Anilide (*b*), m. p. 114°.
n-Amyl chloride	106	—	$0{\cdot}878^{20}_{4}$	Anilide (*b*), m. p. 109°.
tert.-Amyl bromide	107	—	$1{\cdot}198^{18{\cdot}5}_{4}$	
2 : 3-Dichlorobutane	115	—	—	
sec.-Butyl iodide	118	—	$1{\cdot}597^{17}_{4}$	Anilide (*b*), m. p. 108°.
*iso*Butyl iodide	120	—	$1{\cdot}606^{20}_{4}$	*iso*BuHgI (*a*), m. p. 72°; anilide (*b*), m. p. 110°.
*iso*Amyl bromide	120	—	$1{\cdot}220^{17}_{15}$	*iso*AmHgBr (*a*), m. p. 80°.
1 : 3-Dichloropropane	125	—	$1{\cdot}177^{25}_{4}$	
tert.-Amyl iodide	127	—	$1{\cdot}471^{18{\cdot}5}_{15}$	
n-Amyl bromide	128	—	$1{\cdot}218^{20}_{4}$	AmHgBr (*a*), m. p. 122°; anilide (*b*), m. p. 96°.
n-Butyl iodide	130	—	$1{\cdot}612^{20}_{4}$	BuHgI (*a*), m. p. 117°; anilide (*b*), m. p. 63°; *a*-naphthalide (*c*), m. p. 112°.

Ethylene dibromide	131	10	$2{\cdot}190^{17}_{15}$	
2-Bromo-2 : 3-dimethylbutane	[132]	12	$1{\cdot}772^{20}_{0}$	Alcoholic KOH yields tetramethylethylene.
Chlorobenzene	132	—	$1{\cdot}106^{20}_{4}$	Nitration ⟶ *p*-nitrochlorobenzene, m. p. 83°; and *o*-nitrochlorobenzene, m. p. 32°. Further nitration yields dinitrochloro-, m. p. 53°.
Propylene dibromide	142	—	$1{\cdot}933^{20}_{4}$	
Bromoform	147	8	$2{\cdot}890^{20}_{4}$	
*iso*Amyl iodide	147	—	$1{\cdot}515^{18}_{15}$	*iso*AmHgI (*a*), m. p. 122°; anilide (*b*), m. p. 109°.
Acetylene tetrachloride	147	—	$1{\cdot}600^{20}_{4}$	Heating with aq. NaOH or Na_2CO_3 yields $CHCl{:}CCl_2$.
*iso*Butylene dibromide	149	—	$1{\cdot}770^{18}_{15}$	
n-Amyl iodide	154	—	$1{\cdot}510^{28}_{4}$	Anilide (*b*), m. p. 96°.
n-Hexyl bromide	156	—	$1{\cdot}176^{20}_{4}$	Hex. HgBr (*a*), m. p. 119°.
Bromobenzene	156	—	$1{\cdot}522^{0}_{4}$	Nitration ⟶ *p*-nitrobromobenzene, m. p. 123°, and *o*-nitrobromobenzene, m. p. 43°. Further nitration ⟶ dinitro comp., m. p. 73°.
Trichlorohydrin	158	—	$1{\cdot}405^{18{\cdot}5}_{15}$	Excess H_2O at 150° ⟶ glycerol.
o-Chlorotoluene	159	—	$1{\cdot}080^{20}_{15}$	
2 : 3-Dibromobutane	159	—	—	
Tribromoethylene	163	—	$2{\cdot}733^{0}_{4}$	
m-Chlorotoluene	162	—	$1{\cdot}072^{20}_{4}$	
p-Chlorotoluene	162	7	$1{\cdot}069^{20}_{15}$	
Trimethylene dibromide	165	—	$1{\cdot}987^{17{\cdot}5}_{0}$	
*cyclo*Hexyl bromide	166	—	$1{\cdot}329^{15}_{15}$	
m-Dichlorobenzene	172	—	$1{\cdot}288^{20}_{4}$	
p-Dichlorobenzene	173	53	—	2-Nitro-1 : 4-dichlorobenzene, m. p. 54°.
n-Heptyl bromide	179	—	—	
Benzyl chloride	179	—	$1{\cdot}114^{15}_{4}$	
n-Hexyl iodide	180	—	$1{\cdot}439^{20}_{4}$	
Methylene di-iodide	181	4	$3{\cdot}325^{20}_{4}$	
o-Bromotoluene	182	—	$1{\cdot}417^{25}_{4}$	
Trimethylethylene dibromide	70°/30 mm.	7	—	
m-Bromotoluene	184	—	—	
p-Bromotoluene	185	28	—	
Perchloroethane	185	71	—	Camphor-like odour.
Iodobenzene	188	—	$1{\cdot}832^{20}_{4}$	$PhICl_2$, yellow, m. p. 110—136° (dec.); $PhI(Ac)_2$, m. p. 156°; PhIO, m. p. 236° (dec.); Ph_2II, yellow, m. p. 180° (dec.); *p*-nitroiodobenzene, m. p. 172°.
4-Chloro-*m*-xylene	188	—	—	
sec.-Octyl bromide	189	—	—	*β*-Oct.HgBr (*a*), m. p. 39°.
4-Chloro-*o*-xylene	191	—	$1{\cdot}069^{15}_{15}$	
Carbon tetrabromide	[190]	94	—	B. p. 102°/50 mm.
1 : 4-Dibromopentane	197	—	—	
2 : 4-Dichlorotoluene	196	—	$1{\cdot}246^{20}_{20}$	
1 : 4-Dibromobutane	198	—	$1{\cdot}819^{8}_{0}$	
Benzyl bromide	199	—	—	BzHgBr (*a*), m. p. 119°.
2-Bromo-*p*-xylene	200	9	—	
4-Bromo-*m*-xylene	206	—	—	
Benzal dichloride	205	—	$1{\cdot}270^{0}_{4}$	
n-Heptyl iodide	204	—	—	
n-Octyl bromide	204	—	—	
sec.-Octyl iodide	210	—	$1{\cdot}318^{18}_{15}$	
o-Iodotoluene	211	—	—	*o*-$MeC_6H_4ICl_2$, m. p. 85° (dec.); *o*-MeC_6H_4IO, m. p. 175° (dec.).
1 : 2 : 4-Trichlorobenzene	213	17	—	
Benzotrichloride	214	—	$1{\cdot}374^{17{\cdot}5}_{15}$	

TABLE XXIII—*continued.*

Halogen Compounds.

	B. p.	M. p.	*d.*	
4-Bromo-*o*-xylene	214°	—	$1{\cdot}369^{15}_{15}$	
m-Dibromo-*o*-xylene	217	—	$1{\cdot}952^{20}_{4}$	
p-Dibromobenzene	217	89°	—	
1 : 5-Dibromopentane	221	—	$1{\cdot}694^{25}_{4}$	Reaction with amines, see p. 372.
n-Octyl iodide	—	—	$1{\cdot}355^{0}_{4}$	
2 : 5-Dichloro-*p*-xylene	221	71	—	
ω-Bromostyrene	221	7	$1{\cdot}429^{19}_{0}$	Floral odour. Distilled with KOH ⟶ PhC:CH.
o-Dibromobenzene	221	—	$1{\cdot}956^{15}_{4}$	Nitration ⟶ 3 : 4-Dibromo-1-nitrobenzene, m. p. 57°.
2-Bromomesitylene	225	—	—	
2 : 4 : 5-Trichlorotoluene	229	82	—	$CrO_3 2H_2SO_4$ ⟶ trichlorobenzoic acid.
4-Iodo-*m*-xylene	232	—	—	$Me_2C_6H_3ICl_2$, sulphur yellow, m. p. 91° (dec.); $Me_2C_6H_3IAc_2$, m. p. 128°.
2 : 5-Dibromo-*p*-xylene	261	74	—	
2-Iodomesitylene	248	31	—	$Me_3C_6H_2ICl_2$, yellow. $Me_3C_6H_2IAc_2$, m. p. 158°.
Acetylene tetrabromide	—	—	$2{\cdot}964^{20}_{4}$	
4 : 6-Dibromo-*m*-xylene	256	72	—	
α-Chloronaphthalene	263	—	$1{\cdot}194^{20}_{4}$	4-Nitro-1-chloronaphthalene, m. p. 85°; 5-nitro-1-chloronaphthalene, m. p. 216°.
β-Chloronaphthalene	264	60	—	
3 : 4 : 6-Trichloro-*o*-xylene	265	93	—	
1 : 2 : 4-Tribromobenzene	275	44	—	
α-Bromonaphthalene	280	5	$1{\cdot}487^{20}_{4}$	
β-Bromonaphthalene	281	58	—	
Dibromomesitylene	285	60	—	
Benzyl iodide	—	24	—	
Butadiene tetrabromide	—	39	—	
ω-Bromoacetophenone	—	50	—	Oxidation ⟶ benzoic acid.
Styrene dibromide	—	73	—	
m-Xylylene dibromide	—	76	—	Heating with 1 mol. prop. aq. K_2CO_3 ⟶ *m*-xylyleneglycol, m. p. 47°. Aq. alkaline $KMnO_4$ ⟶ *iso*phthalic acid.
o-Xylylene dibromide	—	95	—	Heating with 1 mol. prop. aq. K_2CO_3 ⟶ *o*-xylylene glycol, m. p. 64°.
p-Xylylene dichloride	—	100	—	
4 : ω-Dibromoacetophenone	—	109	—	Oxidation ⟶ *p*-bromobenzoic acid. Reaction with acid salts, see p. 201.
2 : 4 : 5-Tribromotoluene	—	112	—	
Iodoform	—	119	—	Yellow; characteristic odour.
Butadiene tetrabromide	—	117	—	Boils at 260—270° with partial decomposition ⟶ mixture of two isomeric forms, m. p. 117° and 39°. Reduction to butadiene, see p. 368.
p-Xylylene dibromide	245	145	—	
2 : 3-Dibromo-2 : 3-dimethylbutane	—	—	—	M. p. depends on rate of heating, 170—192°. Zn and HAc ⟶ tetramethylethylene.
3 : 5 : 6-Trichloro-ψ-cumene	—	197	—	
3 : 5 : 6-Tribromo-ψ-cumene	—	225	—	
Hexachlorobenzene	322	226	—	
Hexabromobenzene	—	306	—	
Carbon tetraiodide	—	—	—	Dark red crystals; decomposes on heating ⟶ I. Sublime *in vacuo* at 90—100°.

(*a*) For preparation of alkyl mercury salts see Marvel, Gauerke, and Hills, *J. Amer. Chem. Soc.*, 1925, **47**, 309.
(*b*) For the conversion of alkylhalides to anilides of fatty acids see Schwartz and J. R. Johnson, *ibid.*, 1931, **53**, 1063.
(*c*) For the preparation of α-naphthalides of fatty acids from alkyl halides, see Gilman and Furry, *ibid.*, 1928, **50**, 1214.
(*d*) See Mulliken, *Identification of Pure Organic Compounds*, Vol. 4, p. 11.

CHAPTER XI

SULPHONIC ACIDS, SULPHINIC ACIDS, SULPHONES, AND SULPHOXIDES

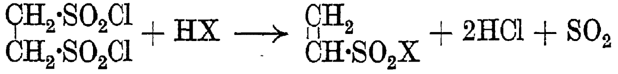
(1) Sulphonic Acids.
  (a) General characteristics.
  (b) Reduction of the Sulphonyl Groups.
  (c) Replacement of the Sulphonyl Group.
    1. By Hydrogen.
    2. By Hydroxyl.
    3. By Cyanide, Carboxyl, Halide, or Amino-Groups.
(2) Sulphinic Acids.
(3) Sulphoxides.
(4) Sulphones.

In this chapter the reactions of the sulphonic acids, sulphinic acids, sulphones, and sulphoxides are considered. The reaction of the mercaptans and thiophenols and thio-ethers are discussed in Chapter III (pp. 106–108 and 114–115).

(1) *Sulphonic Acids.*

(a) *General Characteristics.*—The sulphonic acids are represented by the general formula $R\cdot SO_2OH$ (where $R =$ alkyl or aryl). They are, in general, strong acids, and, unless R has too high a molecular weight, or amino-groups are present, are freely soluble in water. They give rise to salts of the general type $R\cdot SO_2\cdot ONa$, and are converted into sulphonyl chlorides by the action of phosphorus chlorides. The chlorides yield esters and amides by the standard reactions generally applicable to acyl chlorides (pp. 194, 198, 262–264). It is noteworthy that the sulphonyl chlorides in general are comparatively stable to water, and some may be distilled in steam without any serious amount of decomposition. The preparation of the corresponding acids from the sulphonyl chlorides is effected by heating under reflux with aqueous alkali.

Some aliphatic disulphonyl chlorides with the sulphonyl group attached to adjacent carbon atoms behave abnormally. Thus ethane αβ-disulphonyl chloride eliminates sulphur dioxide and hydrogen chloride by reaction with water, alcohol, dry ammonia, or organic amines to furnish derivatives of ethylene sulphonic acid.



$$\begin{array}{l} CH_2\cdot SO_2Cl \\ | \\ CH_2\cdot SO_2Cl \end{array} + HX \longrightarrow \begin{array}{l} CH_2 \\ \| \\ CH\cdot SO_2X \end{array} + 2HCl + SO_2$$

$(X = NH_2, PhNH, HO,$ or $EtO)$

(Autenrieth and Rudolph, *Ber.*, 1901, **34**, 3469; Autenrieth and Koburger, *ibid.*, 1903, **36**, 3626; Kohler, *Amer. Chem. J.*, 1897, **19**, 728; Clutterbuck and Cohen, *J.*, 1922, **121**, 120). Propane αβ-disulphonyl chloride behaves similarly, although if the sulphonyl groups are attached in the αγ positions, normal replacement of the halogen occurs.

(b) *Reduction of the Sulphonyl Group.*—Although the free sulphonic acids, their esters and salts are normally resistant to reduction, the sulphonyl chlorides and sulphonamides can be reduced fairly readily to furnish mercaptans or thiophenols as the final product. Mild conditions of reduction convert sulphonyl chlorides into sulphinic acids:

$$2R{\cdot}SO_2{\cdot}Cl + 2Zn \longrightarrow 2R{\cdot}SO_2Zn + ZnCl_2$$

This can be accomplished by the action of zinc dust on an alcoholic or ethereal solution of the sulphonyl chloride, or by sodium on an ethereal solution of the chloride or by the action of sodium sulphite (Otto, *Annalen*, 1867, **141**, 366; Schiller and Otto, *Ber.*, 1876, **9**, 1585; Autenrieth, *Annalen*, 1890, **259**, 364; Blomstrand, *Ber.*, 1870, **3**, 965; Hilditch, *J.*, 1910, **97**, 1096).

Preparation of Benzenesulphinic Acid.—A solution of 30 g. of benzenesulphonyl chloride in 150 c.c. of ether containing 1—2 c.c. of added water is mixed with 30 g. of zinc dust and heated under reflux for 1—2 hours. The reaction is complete when the mixture becomes pasty and assumes a greyish-white colour. The precipitate, which consists for the most part of the zinc salt of benzenesulphinic acid, is collected, washed with water, and then heated with a solution of 30 g. of sodium carbonate in 150 c.c. of water till the conversion into the sodium salt of the sulphinic acid is complete. The acid is precipitated from an aqueous solution of the sodium salt by adding an excess of sulphuric acid. It is obtained as prismatic crystals, m. p. 83—84°—yield 24 g. (Ullmann and Pasdermadjian, *Ber.*, 1901, **34**, 1151, *footnote*).

Preparation of 2 : 5-Dichlorobenzenesulphinic Acid.—2 : 5-Dichlorobenzenesulphonyl chloride (100 g.) is shaken with a cold solution of sodium sulphite (300 g.) and sodium hydroxide (20 g.) in 1000 c.c. of water. When the sulphonyl chloride has dissolved, the solution is filtered and then acidified with concentrated sulphuric acid. The sulphinic acid which is precipitated (75 g.) is collected by filtration and purified by crystallisation from hot water (Smiles and D. T. Gibson, *J.*, 1924, **125**, 179).

More vigorous conditions, such as the use of zinc and acid, result in the formation of mercaptans from sulphonyl chlorides.

Preparation of Thiophenol.—A fine suspension of benzenesulphonyl chloride (35 g.) in diluted sulphuric acid is obtained by adding the chloride to a mechanically stirred mixture of concentrated sulphuric acid (140 g.) and ice (425 g.) maintained at − 5°. Zinc dust (72 g.) is then added as rapidly as possible without allowing the temperature to exceed 0°, and the stirring is continued for about 1 hour after the addition of all the zinc. The mixture is gradually allowed to warm up spontaneously. A vigorous reaction sets in, which necessitates the use of an efficient reflux condenser. The reduction is completed by boiling under reflux till the solution is clear. It is advisable to continue stirring throughout the preparation.

The thiophenol is driven over from the reduction mixture by distillation in steam, and is isolated from the distillate by extraction with ether. After drying the ethereal solution, the pure product is obtained by fractionation,

b. p. 166—169°—yield about 90% of theory (Adams and Marvel, *Organic Syntheses*, 1921, **1**, 71).

Preparation of p-*Thiocresol.*—A mixture of 20 g. of *p*-toluenesulphonyl chloride, 74 g. of iron filings, and 30 g. of acetic acid is heated on a water-bath and 200 c.c. of 15% hydrochloric acid are added gradually. After heating for 5 hours, the thiocresol is distilled in steam and collected from the distillate by filtration—yield about 50% of theory, m. p. 43° (Decker and v. Fellenberg, *Annalen*, 1907, **356**, 326).

Aryl sulphonamides are smoothly reduced by concentrated aqueous hydriodic acid, preferably containing phosphonium iodide. Thiophenols are formed.

$$CH_3{\cdot}C_6H_4{\cdot}SO_2NH_2 + 7HI \longrightarrow CH_3{\cdot}C_6H_4{\cdot}SH + 6I + NH_4I + 2H_2O$$

Sulphonanilides and some sulphonyl derivatives of amino-acids behave similarly. This method furnishes an alternative to the usual process for the acid hydrolysis of sulphonanilides, and appears to be quite convenient. It has been used successfully for the elimination of the aryl sulphonyl groups from *p*-toluenesulphonyl derivatives of alanine and aniline, benzenesulphonbenzylamide and benzenesulphonamide (E. Fischer, *Ber.*, 1915, **48**, 93).

Preparation of p-*Thiocresol from* p-*Toluenesulphonamide.*—The reducing agent is fuming hydriodic acid (*d*, 1·96) which has been decolorised by shaking with a little phosphonium iodide.

p-Toluenesulphonamide (5 g.) is heated with 50 c.c. of concentrated hydriodic acid and 7 g. of phosphonium iodide in a sealed tube. At about 75° a reaction sets in, as shown by the development of a brown coloration which disappears on shaking. By raising the temperature to 80—85° and shaking the tube frequently, *p*-tolyl mercaptan commences to separate as a feebly-coloured oil. The reaction is complete when the solution develops no colour on standing. This generally requires about 25—30 minutes. The reaction mixture is poured into water (300 c.c.), then cooled to 0° and the thiocresol filtered off—yield 3·1 g., m. p. 44° after crystallisation from dilute alcohol (E. Fischer, *loc. cit.*).

(*c*) *Replacement of the Sulphonyl Group.* 1. *By Hydrogen.*—Substitution of the sulphonic group takes place in either of two directions: (*a*) the elimination of the sulphonic group as sulphuric acid and its replacement by hydrogen, (*b*) replacement by groupings such as $-CN$, $-OH$, $-NH_2$, $-CO_2H$ and the liberation of the sulphonic group as sulphite. These are represented by the equations:

$$R{\cdot}SO_2{\cdot}OH + H_2O \longrightarrow RH + H_2SO_4$$
$$R{\cdot}SO_2{\cdot}OH + NaX \longrightarrow R{\cdot}X + NaHSO_3$$
$$(X = CN,\ OH,\ NH_2 \text{ or } HCO_2)$$

Substitution of the sulphonic group by hydrogen is effected in the aromatic series by heating with concentrated hydrochloric acid in sealed tubes (Limpricht, *Ber.*, 1877, **10**, 315), or more conveniently by heating with diluted sulphuric acid in a current of superheated steam (H. E. Armstrong and Miller, *J.*, 1884, **45**, 148). Phosphoric or hydrochloric acids can be used instead of sulphuric acid. The application of this reaction for obtaining aromatic hydrocarbons and their nitro- and halogen-substitution products is referred to on p. 42.

The temperature at which hydrolysis of the sulphonic acid occurs appears to be determined by the group attached to the sulphonic group. In the following table the temperatures at which hydrolysis becomes appreciable for a few aromatic sulphonic acids are given :

Benzenesulphonic acid .	175°	(Armstrong and Miller, *loc. cit.*)
p-Toluenesulphonic acid	150	
Xylenesulphonic acids .	120	
ψ-Cumenesulphonic acid	115	
Cymenesulphonic acid .	130	
Mesitylenesulphonic acid	100	

It is evident that this method can be used for the separation of some sulphonic acids or for their purification after a preliminary separation from other acids by suitable methods of crystallisation.

2. *Replacement by Hydroxyl.*—This is one of the most important reactions of type (*b*) of the aromatic acids. It is effected by heating a salt of the acid with molten caustic soda or potash. Aliphatic sulphonic acids under these conditions split out the sulphonic group with the formation of olefins.

Preparation of Phenol from Benzenesulphonic Acid.—Potassium hydroxide (35 g.) and 5 c.c. of water are heated together in a silver or nickel basin at about 250°. The melt is stirred by a thermometer, the bulb of which is protected by encasing it in a nickel tube. Powdered sodium benzenesulphonate (18 g.) is added fairly rapidly and the melt stirred continuously, the temperature being maintained at about 230—250°. After about 1 hour the melt is poured on a metal tray and, when cold, is broken up and dissolved in a little water. Acidification of the strongly alkaline solution with concentrated hydrochloric acid causes the separation of phenol as an oil. It is removed from the aqueous solution by means of ether, and the aqueous layer extracted two or three times more with the same solvent. The ethereal extracts are combined, dried in contact with magnesium sulphate, and then fractionated. Pure phenol is collected at 178—182°—yield 6—7 g. (Wurtz, *Annalen*, 1867, **144**, 121; Degener, *J. pr. Chem.*, 1878, [ii], **17**, 396).

Many other monosulphonic acids derived from homologues of benzene and from naphthalene yield phenols under similar conditions, the temperature of fusion being usually kept between 250° and 300°. Disulphonic acids or many phenolsulphonic acids furnish dihydric phenols by a similar process. It is noteworthy that fusion with sodium hydroxide alone fails to furnish phenols from some sulphonic acids, such as *p*-toluenesulphonic acid, although with potassium hydroxide a smooth replacement of the sulphonic group by hydroxyl takes place.

Preparation of p-*Cresol from* p-*Toluenesulphonic Acid.*—Sodium hydroxide (100 g.) and potassium hydroxide (40 g.) are fused together in an iron or nickel crucible and stirred by an iron or nickel tube containing a thermometer. When the temperature of the melt is about 230°, 15 g. of sodium *p*-toluenesulphonate are added. The temperature is now slowly raised, while 45 g. of the sodium salt are stirred in, the additions being made whenever the melt is sufficiently mobile to permit of the solids being stirred in. The temperature is raised to 300°, and then finally to 330°, when the foaming which sets in about 300° should subside. The melt is then poured on an iron tray to cool. The solid is broken up, dissolved in about 600—700 c.c. of water, and acidified with sulphuric acid till there is a distinct odour of sulphur dioxide. The cresol is then distilled in steam. The distillate (600—700 c.c.) is saturated with salt, the cresol which separates is removed, and the aqueous layer extracted with ether. After drying the ethereal solution it is fractionated. *p*-Cresol is collected at 95—96°/15 mm.—yield 60—70% of theory, m. p. 31° (Hartman, *Organic Syntheses*, 1923, **3**, 37).

Preparation of 1 : 7-*Dihydroxynaphthalene*.—The sodium salt of β-naphthol-8-sulphonic acid (64%, 400 g.) is added during 30 minutes to 1200 g. of fused caustic potash at 230—240°. The temperature is then raised to 250° and kept at this point for 30 minutes, the fused mass being thoroughly stirred. The cooled product is broken into small pieces, dissolved in 2800 c.c. of water, and then acidified with 1840 c.c. of concentrated hydrochloric acid. The tar which separates is extracted with chloroform in a Soxhlet. The aqueous solution deposits 1 : 7-dihydroxynaphthalene on cooling, and a further amount is obtained by extracting the aqueous solution with chloroform. The yield of dihydric phenol from the tar and aqueous liquors is about 40%. The pure dihydric phenol is obtained as almost colourless needles by crystallisation from benzene, m. p. 178° (Morgan and Vining, *J.*, 1921, **119**, 1709; Emmert, *Annalen*, 1887, **241**, 371).

The alkali fusion may be accompanied by other reactions. According to Cappelli (*Gazzetta*, 1918, **48**, ii, 107), a small amount of thiophenol may result if the fusion is effected in iron vessels. At high temperatures (320—325°) with sodium benzene sulphonate there may be a small loss due to oxidation (Boswell and Dickson, *J. Amer. Chem. Soc.*, 1918, **40**, 1786). This is far more serious in the alkali fusion of anthraquinone-β-sulphonic acid. Appreciable quantities of alizarin are formed under the normal conditions of fusion, and it is even formed if the sodium salt of anthraquinone sulphonic acid is heated with four times its weight of 20% aqueous caustic soda at 155—165° (Liebermann, *Annalen*, 1882, **212**, 25). 2 : 6- and 2 : 7-Anthraquinonedisulphonic acids undergo a similar oxidation on fusion with caustic soda. It is claimed (Meister, Lucius, and Brüning, D.R.-P. 106,505; F. Bayer & Co., D.R.-P. 197,649) that if the caustic soda is replaced by alkaline-earth hydroxides there is a normal replacement of the sulphonic group without the introduction of hydroxyls in the α position. Alkali fusion of the anthraquinonesulphonic acids may also result in a partial breakdown of the molecule, with the formation of hydroxybenzoic acid, the extent of the disruption being dependent on the conditions (Liebermann and Dehnst, *Ber.*, 1879, **12**, 1290, 1597; Offermann, *Annalen*, 1894, **280**, 17). By the use of alkaline-earth hydroxides instead of caustic soda this disruption is avoided (F. Bayer, D.R.-P. 170,108). Other examples of the disruptive action of alkali fusion are the formation of *o*-toluic acid from naphthalene-1 : 3-disulphonic acid; naphthalene-1 : 3 : 5-, -1 : 3 : 6-, -1 : 3 : 7-, and -1 : 3 : 8-trisulphonic acids yield hydroxytoluic acids (R. Meyer and Hartmann, *Ber.*, 1905, **38**, 3945).

When more than one sulphonic group is present, it is often possible to replace only one of them by suitably modifying the conditions. Thus benzene-*m*-disulphonic acid, which yields resorcinol under the ordinary conditions of alkali fusion, is converted into phenol-*m*-sulphonic acid by heating with dilute sodium hydroxide solution under pressure (Willson and K. H. Meyer, *Ber.*, 1914, **47**, 3160). The selective replacement of a sulphonic group is of some technical importance in the preparation of α-naphtholsulphonic acids. Thus 1 : 5-naphthalenedisulphonic acid furnishes α-naphthol-5-sulphonic acid by the action of caustic soda at 160—190° (Ewer and Pick, D.R.-P. 41,934); α-naphthol-3 : 6-disulphonic acid results by heating naphthalene-1 : 3 : 6-trisulphonic acid with 50% caustic soda at 170—180° (Gürke and Rudolph, D.R.-P. 38,281).

3. *Replacement by Cyanide, Carboxyl, Halide, or Amino-Groups.*—The formation of nitriles occurs when an intimate mixture of a salt of a suitable sulphonic acid and potassium cyanide is distilled. Thus benzene sodium sulphonate and potassium cyanide yield benzonitrile; α-naphthonitrile is similarly obtained from the sodium salt of naphthalene-α-sulphonic acid (Merz and Mülhäuser, *Ber.*, 1870, **3**, 710).

By fusing together sodium formate and the potassium salt of benzenesulphonic acid (the sodium salt gives no yield) a salt of benzoic acid is formed. Salts of α-naphthoic and *iso*phthalic acids are formed in an analogous manner from the appropriate sulphonic acids (V. Meyer, *Annalen*, 1870, **156**, 273).

When sodium benzene sulphonate and sodamide are heated together, aniline is formed in poor yield (Jackson and Wing, *Ber.*, 1886, **19**, 902). Better results are obtained if naphthalene is added to the mixture (F. Sachs, *Ber.*, 1906, **39**, 3014). β-Naphthylamine results from naphthalene-β-sulphonic acid. The replacement is more satisfactory with the naphthol monosulphonic acids which give rise to aminonaphthols (Sachs, *loc. cit.*).

In the anthraquinone series the formation of amino-derivatives from anthraquinonesulphonic acid takes place comparatively readily by heating the acid with aqueous ammonia under pressure in presence of barium chloride or a suitable catalyst. Thus anthraquinone sodium β-sulphonate gives a 70% yield of aminoanthraquinone when it is heated with half its weight of barium chloride and five times its weight of 25% ammonia at 170—177 for 48 hours. The barium chloride may be replaced by manganese dioxide or sodium dichromate. The 1 : 7-, 1 : 6-, 2 : 5-, and 2 : 6-disulphonic acids can be similarly converted into the corresponding diamines (Meister, Lucius, and Brüning, D.R.-P. 267,212 : 273,810; Kaufler and Imhoff, *Ber.*, 1904, **37**, 4708; Badische Anilin u. Soda Fabrik, D.R.-P. 256,515).

The direct replacement of the sulphonic group by halogen in the benzene series does not occur to any serious extent unless amino- or hydroxyl groups are in the *ortho* or *para* position to the sulphonic group, and even in these circumstances the replacement is dependent on the presence of other groups. Although sulphanilic acid can be brominated to 2 : 6-dibromosulphanilic acid in aqueous solution, further bromination yields 2 : 4 : 6-tribromaniline. Replacement of the sulphonic group of 2 : 6-dibromosulphanilic acid by iodine occurs when the acid is treated with iodine monochloride. 4 : 6-Dibromoaniline-2-sulphonic acid suffers an analogous replacement with bromine water or iodine monochloride (Sudborough and Lakhumalani, *J.*, 1917, **111**, 41). In the naphthalene series some nitrosulphonic acids furnish nitrochloronaphthalenes by the action of sodium chlorate and hydrochloric acid (Friedländer, Karamessinis, and Schenk, *Ber.*, 1922, **55**, 45). Under somewhat similar conditions, some of the naphthol- and naphthyl-aminesulphonic acids have the sulphonic group replaced by halogen.

The most commonly applied replacement of the sulphonic group takes place with the anthraquinonesulphonic acids. Thus anthraquinone-α- or -β-sulphonic acids yield the corresponding chloroanthraquinones by treatment in aqueous solution with chlorine at 100°. Dichloroanthraquinones are prepared similarly. A more convenient method consists in boiling the sulphonic acid with hydrochloric acid and sodium chlorate (Ullmann and Ochsner, *Annalen*, 1911, **381**, 2; F. Bayer & Co., D.R.-P. 205,195: 205,913; Badische Anilin u. Soda Fabrik, D.R.-P. 214,714: 228,876).

(2) *Sulphinic Acids.*

The sulphinic acids are represented by the general formula $R{\cdot}SO_2H$ (where R = alkyl or aryl). The free acids are stated to be unstable, pure benzenesulphinic acid slowly changing at room temperature even in the absence of air to yield benzenesulphonic acid and diphenyldisulphoxide.

$$3Ph{\cdot}SO_2H \qquad Ph{\cdot}SO_2{\cdot}OH + Ph{\cdot}S{\cdot}SO_2{\cdot}Ph + H_2O$$

According to Pauly and Otto (*Ber.*, 1877, **10**, 2181) the change is almost complete after 20 months. On the other hand, Autenrieth (*Annalen*, 1890, **259**, 362) states that the pure acid may be kept in a desiccator without change for over a year. The decomposition is accelerated by dilute acids or heating with water at 130° (R. Otto, *Annalen*, 1868, **145**, 317; Pauly and Otto, *loc. cit.*). It is best effected by Hilditch's method of heating with dilute acids (*J.*, 1910, **97**, 1096).

Preparation of 2 : 5 : 2′ : 5′-*Tetrachlorodiphenyl Disulphoxide.*—2 Litres of water containing 2 drops of concentrated sulphuric acid, 10 drops of concentrated hydriodic acid, and 50 g. of 2 : 5-dichlorobenzenesulphinic acid are heated on a water-bath for 4 hours, sulphurous acid being added at intervals to decolorise the solution. The insoluble disulphoxide is collected, triturated with aqueous sodium hydroxide, and the residue crystallised from light petroleum. It separates from this solvent as colourless needles, m. p. 128° (Smiles and Gibson, *J.*, 1924, **125**, 180).

The alkali salts of the sulphinic acids yield sulphones instead of the normal esters by reaction with some alkyl halides and other suitable halogen compounds.

$$R{\cdot}SO_2Na + ClCH_2{\cdot}Ph \longrightarrow R{\cdot}SO_2{\cdot}CH_2{\cdot}Ph + NaCl$$

(Knoevenagel, *Ber.*, 1888, **21**, 1349; Ullmann and Pasdermadjian, *ibid.*, 1901, **34**, 1150; Michael and Palmer, *Amer. Chem. J.*, 1884, **6**, 253; R. Otto, *J. pr. Chem.*, 1889, [ii], **40**, 508).

Preparation of 2-Nitrodiphenylsulphone.—Benzenesulphinic acid (4 g.), *o*-nitrochlorobenzene (4·5 g.) and 2·5 g. of sodium acetate are heated together with about 10 c.c. of alcohol in a sealed tube at 160° for 3 hrs. After cooling, the contents of the tube are washed with water and the insoluble residue of nitrosulphone is crystallised from alcohol, m. p. 147—148°.

The 4-nitrosulphone is prepared similarly, while 2 : 4- and 2 : 4 : 6-trinitrosulphones are obtained by suitable modifications of this process (Ullmann and Pasdermadjian, *loc. cit.*).

The normal esters of the sulphinic acids result by the action of alcoholic hydrogen chloride on the free acid or by the reaction of chlorocarbonic esters on the alkali salts (R. Otto and Rössing, *Ber.*, 1885, **18**, 2506). A more suitable method consists in treating the sulphinic chloride with the appropriate alcohol in presence of potassium carbonate or pyridine (H. Phillips, *J.*, 1925, **127**, 2553). The sulphinic chlorides are best obtained by the action of ethereal thionyl chloride on the sulphinic acid (Hilditch and Smiles, *Ber.*, 1908, **41**, 4113; Phillips, *loc. cit.*).

Sulphinic acids combine additively with αβ-unsaturated acids to form sulphones. Thus cinnamic acid and *p*-toluenesulphinic acid furnish β-phenylpropionic acid β-tolylsulphone.

$$Ph{\cdot}CH{:}CH{\cdot}CO_2H + Tol{\cdot}SO_2H \longrightarrow Tol{\cdot}SO_2{\cdot}CH(Ph){\cdot}CH_2{\cdot}CO_2H$$

The formation of sulphones by the addition of sulphinic acids to quinones is referred to on p. 185. Aldehydes are also able to furnish additive products; those from aliphatic aldehydes are dissociated into their components in solution. Aromatic aldehydes yield more stable products (Kohler and M. Reimer, *Amer. Chem. J.*, 1904, **31**, 163).

$$R{\cdot}CHO + R{\cdot}SO_2H \longrightarrow R{\cdot}CH(OH){\cdot}SO_2{\cdot}R$$

Oxidation of benzenesulphinic acid to the sulphonic acid occurs by treatment with concentrated nitric acid, although some nitration may take place if the acid is too concentrated (R. Otto and Ostrop, *Annalen*, 1867, **141**, 370). Sulphonic acids are also obtained by the oxidation of arylsulphinic acids with potassium permanganate in acetic acid; by this process some disulphone is obtained as a by-product (Hilditch, *J.*, 1908, **93**, 1526).

$$R{\cdot}SO_2H + O \longrightarrow R{\cdot}SO_2{\cdot}OH$$
$$2R{\cdot}SO_2H + O \longrightarrow R{\cdot}SO_2{\cdot}SO_2{\cdot}R + H_2O$$

Aqueous bromine or chlorine converts arylsulphinic acids into the corresponding arylsulphonyl chlorides (R. Otto and Ostrop, *loc. cit.*, p. 372 ; R. Otto, *Annalen*, 1868, **145**, 322).

(3) *Sulphoxides.*

Sulphoxides are formulated R·SO·R′ (R and R′ may be simple or substituted alkyl or aryl groups). As intermediates in the oxidation of sulphides to sulphones they can be oxidised by any of the methods employed for the preparation of sulphones. Fuming nitric acid has been used for this purpose (v. Ofele, *Annalen*, 1863, **127**, 370; 1864, **132**, 87; Saytzew, *ibid.*, 1867, **144**, 150), but it is generally more convenient to use permanganate or hydrogen peroxide (see p. 115).

*Oxidation of Di*iso*amylsulphoxide.*—A suspension of 5 g. of the sulphoxide in 100 c.c. of water heated to 50° is stirred and a hot concentrated solution of permanganate is added as long as there is any decolorisation. After adding sufficient bisulphite to reduce the excess of permanganate, the sulphone is extracted with ether. Di*iso*amylsulphone remains after the solvent has been evaporated, b. p. 295°, m. p. 31° (Beckmann, *J. pr. Chem.*, 1878, [ii], **17**, 441).

Sulphoxides are converted into sulphides by reduction. This can be effected conveniently by dissolving the sulphoxide in acetic acid and warming after the addition of zinc dust. The sulphide is precipitated from the filtered solution by adding water (Saytzew, *Annalen*, 1867, **144**, 153; Gazdar and Smiles, *J.*, 1910, **97**, 2250). Gazdar and Smiles find that by heating in a sealed tube with alcoholic hydrogen chloride at 100°, some nitrohydroxyphenylsulphoxides are smoothly reduced to the sulphide. This method is apparently of limited application, for some sulphoxides (such as benzylsulphoxide) suffer fission under these conditions (Smythe, *J.*, 1909, **95**, 349; compare Pummerer, *Ber.*, 1909, **42**, 2282; 1910, **43**, 1404).

The sulphoxides in general have basic properties, in that they are able to yield chlorides of the type RR′S(OH)·Cl by reaction with hydrogen chloride. Nitrates of the same general type $RR'S(OH)\cdot NO_3$ have been known for some time, and are obtained by the oxidation of the dialkylsulphides with nitric acid. With hydrogen bromide or hydrogen iodide, sulphoxides yield dibromides or di-iodides which are identical with those derived by the addition of the halogen to the sulphide.

$$R'RSO + 2HI \longrightarrow R'RSI_2 + H_2O$$

(Fromm and co-workers, *Annalen*, 1913, **396**, 75; compare K. A. Hofmann and Ott, *Ber.*, 1907, **40**, 4931).

(4) *Sulphones.*

Sulphones have the general formula $RR'SO_2$. They are in general very stable compounds, being indifferent to the usual reducing or oxidising agents, to aqueous acid or alkalis. The stability of the disulphones to alkali appears to depend on the disposition of the sulphone groups. Although disulphones of the type $R'_2C(SO_2{\cdot}R)_2$ are indifferent to alkalis, disulphones such as $R'{\cdot}SO_2{\cdot}SO_2{\cdot}R$ are decomposed by aqueous alkali into a mixture of sulphinite and sulphonate. Disulphones in which the sulphone groups are attached to adjacent carbon atoms are attacked by aqueous alkali with the elimination of one sulphone group.

TABLE XXIV.

Sulphonic Acids.

	M. p.	Phenyl ester. M. p.	Chloride. M. p.	Amide. M. p.	Anilide. M. p.
Methanesulphonic acid . . .	syrup	—	[161°]	90°	99°
Ethanesulphonic acid . . .	hygroscopic cryst. mass	—	[177]	58	55
Benzenesulphonic acid . . .	—	35°	15	149	105
4-Chlorobenzenesulphonic acid .	68°	—	53	144	104
4-Bromobenzenesulphonic acid .	—	—	75	160	119
3-Nitrobenzenesulphonic acid .	—	—	61	162	126
Benzene-*m*-disulphonic acid . .	—	—	63	212	144
o-Toluenesulphonic acid . .	—	52	[126°/ 16 mm.]	155	136
4-Nitro-*o*-toluenesulphonic acid .	$+2H_2O$ 133	64	43	186	148
p-Toluenesulphonic acid . .	—	94	69	137	103
p-Ethylbenzenesulphonic acid .	—	—	12	108	—
o-Xylene-4-sulphonic acid . .	—	—	51	144	—
m-Xylene-4-sulphonic acid . .	$+2H_2O$ 60	—	34	137	—
p-Xylenesulphonic acid . . .	$+2H_2O$ 86	—	24	148	—
ψ-Cumene-5-sulphonic acid . .	$+2H_2O$ 112	—	61	175	—
Mesitylenesulphonic acid . .	$+2H_2O$ 77	—	57	141	—
Cymene-3-sulphonic acid . .	131(*a*)	—	—	151	—
Naphthalene-α-sulphonic acid .	$+2H_2O$ 88	75	67	150	112
5-Nitronaphthalene-α-sulphonic acid	—	—	113	225	—
Naphthalene-β-sulphonic acid .	$+H_2O$ 125	99	76	212	132
Camphor-β-sulphonic acid . .	195 dec.	—	68	170	—
α-Bromocamphor-π-sulphonic acid .	196	—	136	145	—
Anthraquinone-β-sulphonic acid .	—	—	193	261	—
Toluene-2 : 4-disulphonic acid. .	—	—	52	186	189
Toluene ω-sulphonic acid . .	—	—	—	—	104

(*a*) After drying.

APPENDIX

THE IDENTIFICATION OF ORGANIC SUBSTANCES

(1) Preliminary Examination.
(2) Identification of the Elements.
  (*a*) Sodium test for Nitrogen, Halogens, and Sulphur.
    1. Nitrogen.
    2. Halogen.
    3. Sulphur.
  (*b*) Beilstein's Test for Halogen.
  (*c*) Calcium Oxide Test for Halogen.
  (*d*) Tests for Sulphur, Phosphorus, and Arsenic.
(3) Recognition of Characteristic Groups.
  (*a*) Nitrogen, Halogen, and Sulphur Absent.
    1. Carboxylic Acids.
    2. Monohydric Phenols.
    3. Di- and Tri-hydric Phenols.
    4. Aldehydes.
    5. Ketones.
    6. Carbohydrates.
    7. Alcohols.
    8. Esters.
    9. Acetals and Ethers.
    10. Hydrocarbons.
  (*b*) Nitrogen present. Halogen and Sulphur Absent.
    1. Amine Salts.
    2. Acidic Substances.
    3. Amines.
    4. Amides, Nitriles, and other Hydrolysable Substances.
    5. Nitro-compounds, Azo-compounds and Substances Indifferent to Alkali and Acid.
  (*c*) Halogen Present. Nitrogen and Sulphur Absent.
  (*d*) Nitrogen and Halogen Present. Sulphur Absent.
  (*e*) Sulphur Present. Nitrogen and Halogen Absent.
  (*f*) Halogen and Sulphur Present. Nitrogen Absent.
  (*g*) Nitrogen and Sulphur Present. Halogen Absent.
  (*h*) Nitrogen, Halogen, and Sulphur Present.

THE essential part of all identifications consists in inferring from the reactions of the substance what groups are present. It requires therefore, if the deductions are to be of any value, a complete knowledge of the reactions of the compound under examination. The practical operations may be divided into five groups :—

1. Preliminary examination.
2. Identification of the elements present.
3. Examination of the reactions of the substance to ascertain what groups are present.
4. Determination of the physical properties.
5. Preparation of derivatives to confirm the deductions from the evidence obtained in the examination.

(1) *Preliminary Examination.*

The value of a preliminary examination is that it frequently provides clues, which, although not in themselves conclusive, often simplify the subsequent work. A not inconsiderable amount of information may be obtained from such obvious characteristics as colour and odour. Thus when the pure substance is coloured, many classes of compounds are definitely excluded : most hydrocarbons, alcohols, simple aldehydes and ketones, esters, carboxylic acids, and ethers are colourless. On the other hand, all true aromatic azo-compounds are coloured; a nitroso-group in a hydrocarbon residue is frequently associated with a blue or green colour, particularly in the fused state. The occurrence of colour in the aromatic series may also be due to the presence of two such groupings as nitro- and amino- or nitro- and hydroxyl. Where these groups occur together the colour may be modified by salt formation.

The odour of the simple monohydric phenols, the lower aliphatic alcohols, ketones, and aldehydes, the lower fatty acids, aromatic mononitro-compounds is, in general, sufficiently characteristic to afford a clue to their identity. Many esters also can often be recognised by their odour, but it should be remembered that many are odourless. The identification of a type of odour is, however, a matter of experience—it should be noted that the lower members of an homologous series may differ considerably in odour from the higher members.

Whether or not any inferences are drawn from the characteristics of odour, state of aggregation, colour, or appearance, the observations should be recorded as accurately as possible. Indeed, it is necessary throughout the examination to record accurately each observation as soon as made, for the final conclusions must be based on a consideration of all the evidence.

In the preliminary examination the behaviour of the substance towards water should be ascertained—its solubility in cold and hot water—whether it is stable or reacts—and the reaction to litmus. The solubility in ether should also be noted, for this serves to indicate the presence of polyhydroxy-compounds and of complex substances of high molecular weight.

The stability of the substance to heat must also be determined. This is effected by warming a few centigrams of the substance on platinum foil or crucible lid or nickel spatula. The bunsen flame—quite a small one—should be so arranged so that the heat is conducted to the substance along the containing vessel. All changes in appearance as fusion, sublimation, alteration in colour, development of odour, or decomposition should be recorded. If the substance is inflammable, the nature of the flame is often a useful guide, for aromatic compounds and others comparatively rich in carbon burn with a smoky flame. Finally the substance is heated more strongly to oxidise all carbonaceous matter. If after complete ignition a non-volatile residue remains, its composition should be ascertained qualitatively. A carbonate or oxide or a heavy metal indicates the presence of a salt of a carboxylic acid or phenol or a similar acidic substance. A sulphide, sulphite, or sulphate indicates a salt of one of the organic sulphur acids or the bisulphite compound of a carbonyl compound.

The substance should also be heated with soda lime. Many nitrogenous substances will evolve ammonia and vapours alkaline to litmus; hydroxybenzoic acids yield phenols; formates yield hydrogen; simple carboxylic acids yield hydrocarbons.

(2) *Identification of the Elements.*

(a) *Sodium Test for Nitrogen, Halogens, Sulphur.*—This test depends on the formation of sodium cyanide when a carbon compound containing nitrogen is decomposed by heating with sodium; the production of sodium halide from a substance containing halogen; the formation of sodium sulphide from a compound containing sulphur.

The substance is heated in a dry ignition tube with a small piece of sodium. Warm the mixture gently for a few minutes, then raise the temperature gradually to red heat and continue the heating till the decomposition is complete (*note A*). After cooling somewhat, plunge the tube into about 5 c.c. of distilled water contained in a mortar; crush it to coarse powder to facilitate the extraction of the soluble sodium salts, and filter. Divide the filtrate into 4 parts.

1. *Test for Nitrogen.*—A part of the nitrogen in the original substance will be present in the solution as cyanide, and this radicle is tested for by adding a few drops of a concentrated solution of ferrous sulphate, shaking the mixture, and at the same time warming gently (*note B*). After two or three minutes, acidify with dilute hydrochloric acid. The formation of a blue precipitate of Prussian-blue indicates the presence of cyanide in the filtrate from the sodium fusion due to *Nitrogen* in the organic compound under examination (*notes C, D, E*).

Notes (*A*).—If there is any reaction between the sodium and the substance, it should be allowed to go to completion before heating strongly. Should the preliminary tests indicate that the substance is explosive, it is advisable to follow the procedure recommended by Mulliken—namely, to dilute the compound with pure naphthalene and to heat with sodium in an iron tube. As an extra precaution the decomposition should be carried out behind a steel screen.

(*B*).—The solution should be slightly alkaline. The precipitate formed on adding the ferrous sulphate becomes partly oxidised to black ferrosoferric hydroxide during warming and shaking, and thus serves as a source of ferric salt for the production of Prussian-blue. The addition of ferric chloride, which is generally recommended, is not only unnecessary, but the presence of a slight excess of ferric chloride diminishes the sensitivity of the test by masking the faint blue colour when only traces of precipitate are present.

(*C*).—When the amount of Prussian-blue is small, the solution, after acidifying, will have only a faint blue colour, and the appearance of the precipitate will not be obvious. On filtration, however, a blue stain will remain on the filter if the coloration of the solution is due to Prussian-blue. If the blue coloration is very faint, the solution should be left for 10 minutes or so before filtering.

(*D*).—If the substance under examination contains sulphur in addition to nitrogen, a smaller or greater amount of thiocyanate may be formed. This will be recognised by the red coloration which it gives with ferric chloride.

(*E*).—While this test for nitrogen is generally satisfactory, it fails with diazo-compounds and other compounds which lose their nitrogen at comparatively low temperatures. It may also give uncertain results with fairly easily volatile substances which are not reactive, such as tertiary amines.

2. *Test for Halogen.*—A portion of the filtrate from the sodium fusion is acidified with dilute nitric acid and tested for the presence of halide ion by the addition of silver nitrate solution (*Note E*). If a positive indication is obtained, the halogen is identified by the usual qualitative tests. *Iodide* is tested for by the addition of a solution of sodium nitrite to a portion of the solution from the sodium fusion acidified with sulphuric acid. If iodine is liberated, it is extracted with carbon disulphide or chloroform. The aqueous solution after extraction is treated with a small amount of chlorine water. The liberation of bromine occurs if a *bromide* is present. To detect *chloride* a further portion of the filtrate from the sodium fusion is evaporated and the residue subjected to the chromyl chloride test.

Note (*E*).—If the substance has been found to contain nitrogen, the presence of sodium cyanide in the solution will cause the precipitation of silver cyanide, unless the cyanide is first removed by gently boiling with dilute nitric acid for some minutes. In such circumstances, confirm the test for halogen by an application of the calcium oxide test described later.

3. *Test for Sulphur.*—The addition of a very dilute and freshly prepared solution of sodium nitroprusside to the filtrate from the sodium fusion will give a violet coloration if alkaline sulphide is present. This may be confirmed by the lead acetate and by the silver foil tests for sulphide.

Note (*F*).—If the previous tests have indicated the presence of nitrogen in the compound, the examination for sulphide may be unsatisfactory owing to the formation of thiocyanate. It is then necessary to test separately for thiocyanate by the addition of a solution of acidified ferric chloride.

(b) *Beilstein's Test for Halogens.*—A piece of copper wire, bent at the end to form a loop, is freed from traces of halogen by heating in a bunsen flame till it ceases to give a green coloration. While still warm, it is dipped into a portion of the substance under examination and the wire introduced into the base of the bunsen flame. A green or blue coloration usually indicates the presence of *halogen.*

Note (*G*).—Although this method gives satisfactory results with the majority of halogen-containing substances, it also may yield a flame coloration with thiourea and similar compounds, with picolinic acid, quinolinic acid, nicotinic acid, and with many hydroxyquinolines (see Nölting and Trautmann, *Ber.*, 1890, 23, 3664; Milrath. *Chem. Zeit.*, 1909, 33, 1249)

(c) *Calcium Oxide Test for Halogens.*—The substance is mixed intimately with halogen-free lime, transferred to a narrow test-tube, and a further quantity of lime added. Heating is commenced at the upper end of the tube and gradually extended to the mixture until the lower half of the tube is raised to a dull red heat. It is then plunged into water acidified with dilute nitric acid. The resulting solution is tested for halogen in the usual way. This method can be used to confirm the presence of halogen in nitrogenous compounds since nitrogen does not interfere.

(d) *Tests for Sulphur, Phosphorus, and Arsenic.*—When the substance is not volatile, the presence of sulphur, phosphorus or arsenic may be determined by fusion with a mixture of sodium carbonate and potassium nitrate. The melt is dissolved in water and tested for sulphate, phosphate, or arsenate by the usual methods.

(3) *Recognition of Characteristic Groups.*

(a) *Nitrogen, Halogen, and Sulphur Absent.*—The simpler types of compounds to be expected are carboxylic acids, phenols, alcohols, aldehydes, ketones, esters, ethers, and hydrocarbons.

1. *Carboxylic Acids.*—The preliminary observations must be supplemented by further tests.

a. Reaction of the substance toward a cold solution of sodium bicarbonate must be determined. The evolution of carbon dioxide and the neutralisation of the substance usually indicate the presence of an acid. This test is subject to certain exceptions (*Note A*). The presence of a carboxylic acid can only be definitely established when it is shown that it can be recovered unchanged from its solution in sodium carbonate; that it forms derivatives characteristic of carboxylic acids such as acyl chloride, amides, esters, etc. (see Chap. V).

When it is definitely established that a carboxyl group is present, the melting point, boiling point, the qualitative solubility in water, ether, and other organic solvents, and the qualitative solubilities of its more common salts in water should be made. These observations may be supplemented by a determination of the equivalent by titration with standard 0·1*N* alkali (*Note B*).

The type of acid must be ascertained by testing for other characteristic groupings, such as hydroxyl, carbonyl, or ether or ester groups; if the acid is unsaturated, or a dibasic acid capable of forming an anhydride on distillation (*Note C*).

Deductions from the foregoing examination must be confirmed by the preparation of suitable derivatives (see Chaps. V and VI).

Notes (*A*).—The rate of solution in sodium bicarbonate solution of a sparingly soluble acid may be so slow that the evolution of carbon dioxide may not be obvious to a casual observer. The solution of such an acid on keeping and its subsequent precipitation unchanged on acidification with mineral acid are, however, sufficient indication of its acidic nature.

It must be noted, however, that an evolution of carbon dioxide may result from substances other than carboxylic acids, such as easily hydrolysable anhydrides and esters, or phenols containing negative groups.

(*B*).—The physical properties often afford clues to the type of acid. Thus, the lower fatty acids may be recognised by their odour and volatility; the higher fatty acids by their appearance, sparing solubility in water, and by the characteristic behaviour of their alkali metal salts in water. The aromatic acids are nearly all crystalline solids with comparatively high melting points (usually above 100°) and sparingly soluble in cold water.

Some clue to the presence of such hydroxy-acids as tartaric, mucic, saccharic, citric will have been obtained in the preliminary tests. Other hydroxy-acids such as lactic, glycollic, and malic are also readily soluble in water and volatile with difficulty. Other acids soluble in water are the lower dibasic acids—oxalic, succinic, malonic as well as ketonic acids as pyruvic.

(*C*).—Ketonic and aldehydic acids can usually be detected by the formation of phenylhydrazones by reaction in aqueous solution with phenylhydrazine (see p. 216).

Unsaturated acids dissolved in a slight excess of sodium carbonate reduce a cold dilute solution of potassium permanganate immediately. The behaviour towards bromine must also be ascertained (see p. 212).

Ester acids are tested for by refluxing with an excess of alkali, and the products examined as indicated under esters (p. 411).

Ether acids are tested for by heating under reflux for a short time with concentrated hydriodic acid and the mixture gently distilled. The distillate will contain alkyl iodide if an alkoxy-acid is present. The dealkylated acid must be isolated and identified.

2. *Monohydric Phenols.*—Phenol and its homologues are sparingly soluble in water and possess a characteristic type of odour; the hydroxy-derivatives of naphthalene are odourless or almost so.

In the absence of acids, phenols can be recognised by their solubility in dilute sodium hydroxide solution. Very many of them give colorations with ferric chloride. The procedure to be followed is as follows.

(*a*) The substance is suspended in a small volume of water and a few c.c. of 10% sodium hydroxide solution are added. If the substance under examination is a phenol it will dissolve. This should be confirmed by acidifying with dilute hydrochloric acid, when the phenol will be precipitated (*Note A*).

(*b*) Neutral ferric chloride solution is added, and the colour which develops is noted (for exceptions, see Table VI, pp. 118–120) (*Note B*).

(*c*) The identification of a phenol should be confirmed by the preparation of a benzoyl or *p*-toluenesulphonyl derivative by shaking the alkaline solution with benzoyl chloride or with *p*-toluenesulphonyl chloride (see p. 79).

(*d*) Tests must be applied for the presence of other groupings such as alcoholic hydroxyl, carbonyl ester, and ether groupings.

(*c*) The phenol must be characterised, after determination of its boiling point and melting point, by the preparation of suitable derivatives such as toluenesulphonates, benzoates, nitrobenzoates, nitrobenzyl ethers, carbamates, or substitution products as nitro-, nitroso-, or bromo-derivatives (see Chap. III).

Notes (*A*).—Guaiacol and simple hydroxyphenol ethers are comparatively soluble in water.

(*B*).—Enols also yield colours with ferric chloride, but these substances can usually be distinguished by the formation of characteristic copper salts, by their general physical properties, and either by their behaviour on alkaline hydrolysis or towards reagents for the carbonyl group.

3. *Di- and Tri-hydric Phenols.*—The di- and tri-hydric phenols are readily soluble in water, and have no characteristic odour. They are identified by their colour reactions with ferric chloride, their reducing properties, by the formation of esters with acid anhydrides or chlorides and by the preparation of suitable derivatives.

The procedure is as follows.

(*a*) A few drops of neutral ferric chloride solution are added to a solution of the substance in water.

(*b*) In alkaline solution many di- and tri-hydric phenols are oxidised by the air with the development of dark solutions.

(*c*) The substance must be tested for reducing properties towards Fehling's solution and ammoniacal silver nitrate (*Note A*).

(*d*) The presence of hydroxyl should be confirmed by the preparation of an acetate, benzoate, or *p*-toluenesulphonate.

(*e*) Attempts should be made to distinguish between *o*-, *m*-, and *p*-dihydric phenols after the determination of the physical constants. The *para*-compounds are oxidised by mild oxidising agents such as ferric chloride, or dilute acidified chromate to quinones. *m*-Dihydric phenols with a free *para* position give the fluorescein reaction. Many *o*-dihydric phenols give precipitates with basic lead acetate.

Note (*A*).—Reduction of Fehling's solution and of ammoniacal silver nitrate is not specific for polyhydric phenols (compare Morgan and Micklethwait, *J.S.C.I.*, 1902, **21**, 1373). It is consequently of value only when considered in conjunction with other reactions.

4. *Aldehydes.*—The preliminary test for an aldehyde consists in examining the reaction towards Schiff's reagent. The test is carried out as follows.

A few drops of the substance are added to about 3 or 4 c.c. of Schiff's reagent. The development of a pink or red coloration within 2 minutes indicates an aldehyde. If the substance is solid, it is powdered and a few mg. are added to Schiff's solution (*Note A*).

A positive test must be supplemented by examination of the behaviour towards sodium bisulphite solution (p. 125) and Fehling's solution and ammoniacal silver nitrate. Most aldehydes reduce ammoniacal silver nitrate or hot Fehling's solution.

The presence of a carbonyl group must be confirmed by preparation of characteristic derivatives such as oxime, semicarbazone, phenylhydrazone, 2 : 4-dinitrophenylhydrazone, azine, or similar type of compound (pp. 135–138).

The acid derived from the aldehyde by oxidation with permanganate should be isolated and examined.

If the aldehyde under examination is volatile and possesses a powerful and objectionable odour, it is probably a lower aliphatic aldehyde, and can be characterised most conveniently by its *p*-nitrophenylhydrazone or its 2 : 4-dinitrophenylhydrazone.

The aromatic aldehydes are sparingly soluble in water and have in general pleasing odours. They can be characterised quite simply by their phenylhydrazones, semicarbazones, and azomethines (pp. 134–138).

Note (A).—Schiff's reagent must not be warmed, nor must alcohol be used as a solvent.

5. *Ketones.*—In the absence of aldehydes, ketones may be detected by the formation of phenylhydrazones, or of dinitrophenylhydrazones. Low-boiling ketones of the aliphatic series require the use of *p*-nitrophenylhydrazine or of 2 : 4-dinitrophenylhydrazine for the production of solid hydrazones.

The aliphatic ketones containing the group $CH_3{\cdot}CO-$ and also cyclic ketones dissolve in bisulphite solution with the evolution of heat to form bisulphite compounds (p. 125).

Ketones may be further characterised by the preparation of oximes and semicarbazones.

Note.—All reducing sugars will give a reaction with phenylhydrazine, but their physical properties and some of their reactions serve to distinguish them from other carbonyl compounds.

6. *Carbohydrates.*—Some indication of the presence of a sugar will have been obtained in the earlier tests, as charring with concentrated sulphuric acid with the evolution of carbon monoxide, carbon dioxide, and sulphur dioxide; and also by the behaviour on heating. Many natural glucosides give an intense coloration with concentrated sulphuric acid, although many other substances also give such colorations, *e.g.*, triphenyl carbinol and similar compounds, benzilic acid.

The following tests should be made.

(*a*) Ascertain the action of Fehling's solution on the original substance before and after hydrolysis with dilute hydrochloric acid.

(*b*) The product of the action of phenylhydrazine should be isolated and its physical properties examined. When the original substance only reduces Fehling's solution after hydrolysis with dilute acid, the action of phenylhydrazine on the hydrolysed sugar should be ascertained.

(*c*) Determine the optical activity in aqueous solution. If a reducing sugar is present, the mutarotation should be determined. The effect of hydrolysis with dilute acid on the optical rotation should also be determined.

(*d*) The sugar is characterised by its acetyl derivative prepared by acetylation in pyridine or by heating with acetic anhydride and sodium acetate. A suitable hydrazone or osazone should be prepared. When the results of hydrolysis indicate the presence of a glucoside or of a di- or poly-saccharide, the fission products should be separated and identified by the preparation of suitable derivatives.

7. *Alcohols.*—The identification of the alcoholic hydroxyl group depends on the formation of esters by reaction with acid chlorides or anhydrides, and on the formation of alcoholates with metallic sodium. In addition, the nature of the alcohol, whether primary, secondary, or tertiary, must be ascertained.

The procedure to be followed is as follows.

(*a*) A thin bright slice of sodium is added to the dry alcohol. Solution of the metal accompanied by the evolution of hydrogen indicates, in the absence of phenols and acids, an alcohol. This test is of value only when the substance is perfectly dry. It is essential to dry the compound before this test, by keeping it in contact with solid potassium carbonate for some time. When the substance under examination is a solid, it should be dissolved in dry benzene or dry ether (dried over sodium) or some other non-hydroxylic solvent.

(*b*) As many esters react with sodium, this test must be supplemented by observations of the behaviour of the substance towards acid chlorides and anhydrides.

1. Add to a small quantity of the alcohol, cooled in running water, about an equal volume of freshly distilled acetyl chloride. A vigorous reaction ensues with the evolution of hydrogen chloride, and on pouring into water the odour of an ester should be apparent if a simple monohydric alcohol of comparatively low molecular weight is present. The products of the reaction should be isolated and the physical properties ascertained.
2. The test is repeated with acetic anhydride. There is a rise in temperature if an alcohol is present, and the reaction is completed by warming. On diluting with water, the odour of an ester may be apparent. The product formed should be isolated and its physical properties ascertained.

When any doubt exists about the reaction of the substance with acid chlorides or anhydrides, the reaction should be repeated, using pyridine as a solvent (p. 79).

If the ester formed in the above tests is not solid, attempts must be made to obtain a crystalline derivative by reaction with nitrobenzoyl chloride, or with phenylcarbimide, naphthylcarbimide, or xenylcarbimide. Some polyhydric alcohols give crystalline benzoates.

(*c*) *The Type of Alcohol.*—Oxidation converts primary alcohols into aldehydes, secondary to ketones. This can be effected conveniently by distilling gently with a dilute solution of potassium dichromate which has been acidified with sulphuric acid. The products should be isolated and characterised.

Tertiary alcohols are best identified by the ease with which they are converted into chlorides by warming with concentrated hydrochloric acid, and the subsequent behaviour of the chloride (see p. 84).

(*d*) Determine the physical properties.

(*e*) Unless the alcohol has been definitely identified in the foregoing tests, it should be examined further for the presence of ester or ether groupings, by submitting a portion to hydrolysis with caustic soda solution; and a second portion to the action of concentrated hydroiodic acid.

8. *Esters.*—The suspected ester is heated under reflux with about five times its bulk of 20% aqueous sodium or potassium hydroxide

until decomposition is complete. The time taken for hydrolysis is dependent on the nature of the ester. Thus while the alkyl esters of oxalic acid suffer partial hydrolysis even in cold water, the esters of the *ortho*-substituted benzoic acids are very resistant.

Note.—When the substance under examination is not odourless, some guide to the progress of the hydrolysis is afforded by the change in the intensity of the odour, or of its nature. When the alcohol is soluble in 20% aqueous alkali the disappearance of the ester layer is an indication that the hydrolysis is complete.

The hydrolysed product is now examined for an alcohol or phenol and an acid.

(a) *The Isolation of the Alcohol or Phenol.*—Alcohols volatile in steam are recovered by distilling. A portion of the distillate is tested by the iodoform reaction for the presence of such alcohols—ethyl, *iso*propyl, *sec.*-butyl, etc.—as give this test. The first few c.c. of the distillate, if homogeneous, are saturated with potassium carbonate, and if there is a separation into two layers, the upper layer is removed, dried over potassium carbonate, and characterised by the formation of a *p*-nitrobenzoate or 3 : 5-dinitrobenzoate. If the distillate is turbid owing to the presence of a sparingly soluble volatile alcohol, it is removed after saturating the distillate with salt or potassium carbonate. It should be thoroughly dried before determining the physical properties, as many of the aliphatic alcohols, sparingly soluble in water and of comparatively low molecular weight, form constant-boiling mixtures with water.

2. High-boiling alcohols not volatile in steam may be removed by extraction with ether.

3. If no positive results have been obtained in the previous tests, the hydrolysed solution should be examined for the presence of a phenol by saturating with carbon dioxide and extracting with ether. The ethereal extract is examined for phenols in the usual way.

4. In the absence of any definite indications of the presence of an alcohol or phenol, tests for polyhydric alcohols may be deferred until the acid has been removed, if it is sparingly soluble in water, or until its type has been ascertained.

(b) *Identification of the Acid.*—A portion of the alkaline solution free from monohydric alcohol or phenol is acidified with dilute hydrochloric acid.

1. A precipitate or an oily suspension indicates the presence of an aromatic acid or of a sparingly soluble aliphatic acid. The acid is separated and identified.

2. If no precipitate forms, a portion of the acidified solution is distilled and the distillate examined for organic acids volatile in steam.

3. In the absence of any positive results in the previous tests, a portion of the acidified solution is extracted with ether, and the ethereal solution, after drying over anhydrous magnesium sulphate, is evaporated.

4. Tests are finally applied for non-volatile acids soluble in water and not readily extracted from aqueous solution by ether. Some of the alkaline solution from the hydrolysis is acidified with acetic acid and tested for oxalic acid by the addition of a solution of calcium chloride. Another portion is carefully neutralised with hydrochloric acid, and a solution of calcium chloride added to precipitate acids yielding sparingly calcium salts. If no precipitate forms even on boiling, the effect of adding barium chloride, cadmium chloride, or other suitable metal chlorides should be ascertained; attempt to precipitate the lead salt by the addition of lead acetate to some of the hydrolysed solution neutralised with nitric acid. If a precipitate is produced by these methods, it must be examined for the acid, and where possible the acid isolated from it.

Some few acids are not readily precipitated from aqueous solution as sparingly soluble salts, nor are they readily extracted from aqueous acidified solutions by ether. Of these, lactic is the most important, and tests should be applied for this acid. It is best isolated by acidifying, and then absorbing the solution in powdered plaster of paris. The mass so formed is broken up and extracted by ether in a Soxhlet.

5. If the presence of an alcohol has not been detected in the previous tests, the presence of a polyhydric alcohol may be suspected. Indications of this will have been derived from a knowledge of the acid present, and the physical properties of the original ester. The polyhydric alcohol is isolated, after removing acids soluble in ether or sparingly soluble in water, by evaporating the neutralised solution to dryness under diminished pressure, and then extracting with ethyl acetate. Removal of the solvent leaves as residue the polyhydric alcohol, which can be identified by its physical characteristics, and by the preparation of suitable derivatives.

9. *Acetals and Ethers.*—(a) *Acetals.* Warm with dilute hydrochloric acid, and test for the presence of aldehydes. If a positive indication is obtained, the alcohol and aldehyde should be characterised by the preparation of suitable derivatives.

(b) *Ethers.* The substance is refluxed with concentrated hydroiodic acid and then distilled. Alkyl iodides will be obtained from aliphatic ethers and from alkyl aryl ethers. The identification of the products of fission and the physical properties of the original substance serve to identify the ether. The aryl alkyl ethers may, in addition, be characterised by the preparation of nitro- or bromo-substitution products.

The true aromatic ethers, of which diphenyl ether is an example, are stable to hydroiodic acid, and must be dealt with under hydrocarbons.

10. *Hydrocarbons.*—For the purpose of identification, the hydrocarbons may be divided into three broad groups—unsaturated hydrocarbons, paraffins and saturated stable cyclic hydrocarbons, and aromatic hydrocarbons.

The results of the preliminary tests often permit a rough classification. Thus benzene and many of its homologues and terpenes may be recognised by their odour, while many of the polycyclic aromatic hydrocarbons are characterised by their comparatively high melting point and sparing solubility.

(a) *Unsaturated hydrocarbons* are tested for by

1. Baeyer's test (p. 4).

2. Decolorisation of bromine water or of a solution of bromine in carbon tetrachloride. (For exceptions see p. 26.) In addition, the behaviour towards ammoniacal cuprous chloride or silver nitrate should be ascertained in order to detect a grouping $-C{\vdots}CH$.

Physical properties, such as boiling point, melting point, density, and refractive index, should be determined before characterising the hydrocarbon. The physical constants of the product of the addition of bromine should also be determined.

The further characterisation of the simple olefines may be effected by conversion into alkyl bromides by the action of hydrogen bromide, or into alcohol by the action of sulphuric acid of suitable concentration. Terpenes are usually characterised by the formation of hydrochlorides, hydrobromides, nitrosyl chlorides, and similar compounds (see pp. 17–23). When the identity of the unsaturated hydrocarbon is not established definitely by these tests it is advisable to ascertain the products of oxidation with permanganate, or if necessary with ozone or benzoyl hydrogen peroxide. Titration with bromine in carbon disulphide or carbon tetrachloride or catalytic hydrogenation is often useful in determining the number of unsaturated linkings.

(b) *Hydrocarbons of the benzene and naphthalene series* will react with fuming sulphuric acid (15–20% SO_3) to yield sulphonic acids, and this is shown by the solution of the hydrocarbon in the acid.

2. Nearly all hydrocarbons of this series yield nitro-compounds by reaction with nitric acid in presence of sulphuric acid, and the formation of such compounds serves also to characterise the hydrocarbon.

3. Other derivatives which can serve to identify the hydrocarbon are sulphonyl chlorides and amides; in a few instances, picrates; and (where there is a side-chain) oxidation with alkaline permanganate or chromic acid will give a carboxylic acid (p. 34).

(c) *Polycyclic hydrocarbons*, as anthracene, phenanthrene, and similar substances, are best characterised by their picrates, and by the products of oxidation (see pp. 60, 61).

(d) *Paraffins and Derivatives of* cyclo*Hexane*.—In the absence of reactions indicating any hydrocarbons of the foregoing groups, the presence of a paraffin or of a derivative of *cyclo*hexane can be assumed. The identification of the hydrocarbon depends on its physical properties—boiling point, melting point, density, and refractive index.

(b) *Nitrogen Present, Halogen and Sulphur Absent.*

The following types of compounds are to be expected; amines either free or as salts, ammonium salts, acids or esters containing nitrogenous groups, amides, imides, nitriles, compounds containing nitro-, nitroso-, azo-, or azoxy-groups, nitrogenous heterocyclic compounds, oximes, semicarbazones, hydrazones, and similar compounds, azides, esters of nitric and nitrous acids.

1. *Amine Salts.*—If a salt is present, the addition of a cold solution of sodium hydroxide will result in—

either (*a*) the separation of a base, sparingly soluble in water, resulting from a salt of an aromatic amine or of an aliphatic amine of comparatively high molecular weight. These two classes of amines are readily distinguished by their action to litmus and other reactions (pp. 259–260).

or (*b*) there is no separation, but the amine is recognised by its odour and by its action on moist red litmus suspended above the solution. This indicates a salt of ammonia or of an aliphatic amine.

(*c*) If there is no apparent liberation of a base, the alkaline solution should be extracted with ether. The physical properties of any material which may be extracted are compared with those of the original substance (*Note A*).

The base liberated from the salt must be isolated and identified according to the procedure outlined later.

Note (*A*).—The salts of amino-esters yield the free ester on cautious treatment with cold alkali. Subsequent extraction with ether may remove the free ester, but the success attending such an operation depends on the type of amino-ester, on the precautions taken to prevent hydrolysis of the ester, and also on the solubility of the ester.

Amino-acids may also be present as salts of inorganic acids or combined with picric acid. Although the addition of alkali decomposes such salts, the amino-acid is not extracted from the alkaline solution. Aminophenols are similarly liberated from their salts by the addition of alkali, but are not extracted from alkaline solution by ether. Such alkaline solutions darken on keeping.

Quaternary ammonium salts give no base on treatment with aqueous alkali. They may be recognised by the formation of a strongly alkaline solution on treatment with moist silver oxide. From such a solution a tertiary amine can be obtained by distillation.

2. *Acidic Substances.*—If there is no indication of the presence of an amine salt, the ready solubility in sodium hydroxide of a substance sparingly soluble in water suggests the presence of an acidic substance. Solubility in alkali is, however, not only a property of nitro- and amino-carboxylic acids, but also of nitro- and nitroso-phenols, of primary and secondary nitro-compounds, of oximes, and of some amides and imides.

Nitro- and nitroso-phenols can generally be distinguished by the development of highly coloured solutions in alkali. It should also be noted that some polynitro-aromatic compounds show a slow development of dark surface layers on the solid in contact with concentrated alkali.

In order to distinguish comparatively strong acids, it is advisable to examine the behaviour towards sodium bicarbonate solution. If this test indicates the presence of a comparatively strong acid by the liberation of carbon dioxide in the cold, a titration against standard alkali using phenolphthalein will often give useful information. This must be followed by a further examination to ascertain the nature of the other groups present, and also by the preparation of derivatives which are characteristic of these groups.

3. *Amines*.—(a) *Test for basicity*. The presence of the lower aliphatic amines will have been indicated in the preliminary tests by their odour and their alkaline reaction towards litmus. This should be confirmed by showing that they neutralise hydrochloric acid, preferably by a rough micro-titration against standard acid using methyl-orange as indicator.

With aromatic amines and some heterocyclic substances, which have no action on red litmus, the titration should be carried out using congo-red paper as an external indicator (compare Mulliken, *The Identification of Pure Organic Compounds*, Vol. 2, p. 9).

When the original substance is insoluble in water, the solution of the compound in dilute acid or the precipitation of a salt is sufficient indication of the presence of a base, provided that it is shown that the substance is recovered unchanged by the addition of an excess of dilute alkali.

Note.—These tests give definite results only with definitely basic compounds. There are many amino-compounds as diphenylamine, its homologues and derivatives, nitranilines and similar compounds, the salts of which are extensively hydrolysed in aqueous solution. It is necessary, therefore, to ascertain qualitatively the solubility of the substance in 5*N*-hydrochloric acid and in concentrated hydrochloric acid. In addition, an ethereal solution of the substance should be shaken with 2*N*- and 5*N*-hydrochloric acid to determine if any of the substance passes into the acid layer.

It must be noted that solubility in concentrated hydrochloric acid alone is no indication of the presence of a base, for many compounds, *e.g.* anilides, amides, nitriles, can combine with hydrochloric acid under these conditions.

(b) *Action of Nitrous Acid*.—The tests for basicity should be followed by an examination of the behaviour of the substance towards nitrous acid.

The substance, dissolved or suspended in 5*N*-hydrochloric acid—about 3 or 4 mol. proportions is usually sufficient—is cooled in ice-water and *N*-sodium nitrite solution added drop by drop till a very slight excess is present as shown by the starch iodide test. Even a moderate excess of nitrous acid must be avoided.

The changes which may occur in the solution should be observed exactly.

1. If the previous tests indicated an aliphatic amine, the evolution of a gas would afford reasonable confirmation.

These indications should be followed up by the preparation of the toluenesulphonyl, benzenesulphonyl, or naphthalenesulphonyl derivative, see pp. 262–267. Solubility of the derivative in aqueous alkali would confirm the identification of a primary amine. It could then be characterised by the preparation of other suitable derivatives, see pp. 263, 266, 272, also Tables XV, XVI, and XVII.

Note.—The evolution of nitrogen must not be taken as evidence of the presence of a primary aliphatic amine without other confirmatory evidence, since amides of the type R·CONH$_2$ give nitrogen by reaction with nitrous acid.

Aliphatic amino-acids also yield nitrogen under similar conditions. They can be recognised by their ability to form metal salts, some of which are characteristic, *e.g.*, the copper salt. They also form acyl derivatives. In addition, they can be titrated normally against alkali in alcoholic solution using phenolphthalein.

2. The formation of a turbidity or the separation of an oil or solid may be due to the formation of a nitrosamine resulting from a secondary amine. In these circumstances the solution is extracted with ether, the ethereal solution freed from all traces of nitrous by washing with alkali, and dried. A portion after evaporation of the solvent is submitted to the Liebermann test (see p. 327). A positive result should be confirmed by the preparation of the arylsulphonamide.

If the Liebermann test is negative, the formation of the oil may be caused by the reaction of the nitrous acid with phenylhydrazine or its nuclear-substituted derivatives. This can be confirmed by the determination of the behaviour of the original substance towards carbonyl groups and by the action of mild oxidising reagents.

3. The formation of a red or brownish solution, often accompanied by the separation of a crystalline solid, indicates the formation of a *para*-nitroso-compound from a tertiary aromatic amine with a free *para* position. This can be readily confirmed by the isolation of the green or blue free nitroso-base by the cautious addition of cold dilute alkali.

Such tertiary amines can be characterised by the formation of a picrate, or a quaternary ammonium salt by the action of methyl iodide, as well as by the *p*-nitroso-compound when this is solid.

4. In the absence of any obvious reaction, a portion of the solution treated with nitrous acid is poured into a solution of (*a*) β-naphthol in dilute alkali, (*b*) an alkaline solution of R salt.

The formation of a highly coloured precipitate from (*a*) and a highly coloured solution from (*b*) indicates the presence of a diazotisable primary amine.

The presence of a primary amine should be confirmed by the preparation of an arylsulphonyl derivative yielding an alkali salt. The identification of the amine can be completed by a determination of its physical constants and by the preparation of other suitable derivatives.

5. Tertiary amines, except aromatic ones containing a free *para* position, are indifferent to nitrous acid under the conditions prescribed. They can be recovered unchanged. The presence of a tertiary amine cannot, however, be considered to have been proved until the basic properties of the substance have been fully established by the preparation of salts; until it has been shown to be indifferent to acyl chlorides and anhydrides: that it reacts with methyl iodide to yield quaternary ammonium salts.

6. Unless the identification of the amine has been established definitely by its reactions and physical constants and by its deriv-

atives, the examination should be continued for groups other than those already tested for: such groups are amide, nitrile, ester, carbonyl, nitro and other reducible groups.

Note.—The aromatic amines containing one nitro-group in the nucleus are coloured yellow, orange, or red, and form salts which are colourless when not hydrolysed. After establishing the presence of an amino-group, the nitro-group can be tested for by reduction and subsequent diazotisation. When the original substance contains a primary amino-group, it should be acetylated and reduced in boiling alcoholic solution with zinc dust before further treatment with nitrous acid.

The di- and tri-nitroamino-compounds do not diazotise regularly under the usual conditions. They are best recognised by their behaviour towards hot alkaline solutions.

Aminoazo-compounds are also highly coloured, but they form coloured salts. They are recognised by yielding a mixture of amines on reduction.

4. *Amides, Nitriles, and other Hydrolysable Substances.*—(a) *Alkaline hydrolysis.* The substance is heated under reflux with 5*N*-sodium hydroxide solution. The solution is subsequently examined for ammonia or volatile amines by distillation, and also for alcohols resulting from the hydrolysis of amide esters. The alkaline residue is examined for the organic acid (see p. 412).

When thus hydrolysed, simple amides and nitriles are converted into the sodium salt of the corresponding acid with the liberation of ammonia. Alkyl-substituted amides behave similarly.

Note.—*o*- and *p*-Nitrophenyl alkyl ethers are hydrolysed more or less rapidly by aqueous alkali to nitrophenols.

(b) *Acid hydrolysis.* A number of amides, particularly those derived from the arylamines, are only slowly decomposed by aqueous alkali. They are more susceptible to acid hydrolysis. Consequently if alkaline hydrolysis gives negative results, the behaviour towards hot 20% hydrochloric acid, concentrated hydrochloric acid, approximately 30% sulphuric acid, or concentrated sulphuric acid should be ascertained. Preliminary experiments should be made in test tubes before deciding on the most suitable concentration of acid. The hydrolysis is completed by warming under reflux.

1. A portion of the solution is warmed with Fehling's solution. Reduction indicates the presence of an oxime, semicarbazone, hydrazone, or some similar compound. The ketone or aldehyde resulting from the hydrolysis should be isolated and characterised.

2. A second portion of the solution is made alkaline. The liberation of an amine indicates a *N*-substituted amide; identification of the amine and of the acid from the hydrolysis establishes the identity of the amide, which should be confirmed by determining the physical constants of the original substance.

The liberation of ammonia indicates a nitrile stable to alkaline hydrolysis, and here also the acid must be isolated and identified.

Note.—Arylhydrazines sparingly soluble in water will also be set free on the addition of alkali, but an indication of their presence will have been obtained in the earlier tests.

Nitrous esters and nitrosamines will yield nitrous fumes on treatment with acids, but of these the nitrous esters will have been detected earlier.

5. *Nitro-compounds, Azo-compounds, and Substances Indifferent to Alkali and Acid.*—The substance is reduced by tin and acid.

About 0·5—2 g. of the substance is added to about three times its weight of tin; 5—10 times its weight of hydrochloric acid is then added gradually. The reaction is completed by warming. An excess of alkali is added till the precipitated hydrated tin oxide is dissolved, and after cooling, extract with ether. The ethereal solution is evaporated and tested for a diazotisable amine. An aromatic primary amine results from a nitro-, azo-, azoxy-compound, or an arylhydroxylamine.

The physical properties of the substance, together with such additional reactions as they may suggest, will usually enable a decision to be made as to the type of compound present.

(c) *Halogen Present, Nitrogen and Sulphur Absent.*

The more common types of compounds likely to be present are the halogen-substituted hydrocarbons, ethers, alcohols, aldehydes, ketones, phenols, acids, and their derivatives.

The preliminary observations may afford valuable clues. Thus lachrymatory odours are associated with some of the halogen ketones, benzyl halides and their homologues, and with many aroyl halides. Many of the halogen-substituted hydrocarbons have odours which are readily recognised. Solubility in water usually indicates a substance of comparatively low molecular weight containing $-CO_2H$, $-OH$, $-CHO$ groups. An acid reaction in water does not necessarily imply the presence of an acid. It may be due to the partial hydrolysis of an acid chloride, or an ester, or to an unstable halogen-substituted compound, or to a halogen phenol.

A vigorous reaction with water resulting in the liberation of halogen hydride indicates a fatty acyl halide. Such an observation should be followed up by identifying the products formed, and by observing the reaction towards alcohols and aniline, and isolating the resulting products. The reaction with aniline can be carried out in benzene or ether solution, when a precipitate of aniline hydrochloride will be formed. The benzene solution after the removal of excess of aniline will give an anilide.

1. *Action of Aqueous Solutions of* (a) *Sodium Bicarbonate,* (b) *Sodium Carbonate,* (c) *Sodium Hydroxide.*—A distinction can be made between neutral and acidic substances by the action of cold sodium bicarbonate solution. Among the classes of substances which decompose bicarbonates and carbonates are acids, halogen-substituted phenols, and those substances which suffer hydrolysis in water.

The presence of an acid can only be considered to be established when it is shown to be recovered unchanged from its sodium salt, and subsequently convertible into an acid chloride, amide, or ester.

The halogen-substituted phenols are precipitated unchanged from their sodium salts, and can be recognised by the formation of acyl derivatives. Many also give nitro- and bromo-substituted products.

The effect of heating with 5*N*-sodium hydroxide under reflux should always be determined. A portion of the hot solution should be removed at intervals, acidified with dilute nitric acid, and tested for halidion. The absence of any positive result, even after prolonged heating, indicates that the halogen is substituted in an aromatic nucleus. Aliphatic halogen compounds and those aromatic compounds containing halogen in a side-chain give rise to sodium halide on heating with sodium hydroxide.

Whether or not there has been any formation of sodium halide, the product should always be examined for (*a*) alcohols resulting from the hydrolysis of esters or of some monohalogen compounds or from the action of the alkali on some aromatic aldehydes resulting from the hydrolysis of substances of the type $Ar{\cdot}CHCl_2$; (*b*) acids from the $-CCl_3$ group, or from esters, or from the Cannizzarro change of some aromatic aldehydes; (*c*) unsaturated compounds from the elimination of the elements of halogen hydride.

The original substance should also be examined for alcoholic hydroxyl groups and for carbonyl groups by the usual methods. If positive results are obtained, they must be confirmed by the preparation of appropriate derivatives.

2. In the absence of any characteristic groups except halogen, the characterisation of the compound depends on the results of the previous tests. With aromatic halogen-substituted hydrocarbons, nitration, sulphonation, or further substitution of halogen are the usual methods of supplementing the information derived from the reactions and physical constants. Alkyl halides may be characterised by the replacement of the halogen by suitable groupings such as hydroxyl, arylamino, etc. With polyhalogen aliphatic compounds the procedure depends on the results of the treatment with alkali.

(d) *Nitrogen and Halogen Present, Sulphur Absent.*

The more common types of substances to be expected are salts of amines and amino-esters, halogen-substituted amines, amides, nitriles, nitro- and azo-compounds, acids and esters, phenols, aldehydes and ketones containing nitro- and halogen groups, nitro-substituted acid halides, as well as oximes, hydrazones, semicarbazones of halogen-substituted ketones and aldehydes.

The substance is submitted to the tests outlined in section (b) for (*a*) amine salts, (*b*) acidic substances, (*c*) amines, (*d*) substances hydrolysed by alkali, (*e*) substances hydrolysed by acid, (*f*) neutral substances reducible to primary amines. In addition, carbonyl, alcoholic hydroxyl, and ether groups must be tested for.

Notes (*A*).—The salts may be halogen hydride salts of unsubstituted amines, or they may be derived from halogen-substituted amines. The amine should be isolated, and tested for halogen before determining its class. The acidic component should also be identified whenever possible by isolating it according to the scheme outlined on p. 412.

(*B*).—Although the monohalogen-substituted aromatic amines are basic enough to form salts with aqueous hydrochloric acid, the basic properties are very considerably reduced by the presence of more than one halogen in the nucleus. The polyhalogen-substituted primary aromatic amines diazotise only under special conditions (see p. 283).

(*C*).—The substances hydrolysed by hot alkali include not only amides and nitriles, esters of amino- and nitro-substituted acids, but also the chlorides of nitro- and acylamino-acids. Many nitro-halogen-substituted aromatic compounds are also attacked by alkali with the formation of nitrophenols (see p. 54).

(e) *Sulphur Present, Nitrogen and Halogen Absent.*

The following types of compounds may be expected—mercaptans, thio-ethers, disulphides, thio-acids, sulphonic acids and sulphinic acids and their esters, sulphones, sulphoxides, the bisulphite compounds of aldehydes and ketones, alkyl-sulphites and -sulphates.

The odours of many thio-ethers and some thio-acids and most mercaptans are objectionable and persistent, and consequently the presence of these compounds cannot easily be overlooked.

1. When an inorganic residue is left on ignition, the examination is restricted to substances yielding salts, as acids, bisulphite compounds, or mercaptans.

In these circumstances the substance is acidified with hydrochloric acid.

(*a*) The evolution of sulphur dioxide in the cold indicates a bisulphite compound. The aldehyde or ketone is liberated by warming with sodium carbonate solution or dilute hydrochloric acid, and identified by the usual methods.

(*b*) Some thio-acids liberate hydrogen sulphide.

(*c*) The liberation of mercaptan may arise from the salt of a mercaptan or from a salt of thiosulphuric esters of the type

$$\mathrm{NaO{\cdot}SO_2{\cdot}SAlk.}$$

(*d*) The formation of sulphuric acid on warming, as shown by the gradual development of a precipitate of barium sulphate on adding a solution of barium chloride, indicates that the salt of an alkyl hydrogen sulphate is present. The alcohol should be liberated by distillation with dilute hydrochloric acid and identified.

(*e*) If there is no development of sulphuric acid or the liberation of a volatile compound, a salt of sulphonic acid or a thiosubstituted acid is indicated.

2. If the substance is not a salt, it is classified either as (*a*) neutral or (*b*) acidic by its reactions towards cold dilute solutions of sodium carbonate and sodium hydroxide.

(a) *Acidic substances* include sulphonic acids, thio-acids, and mercaptans.

The unsubstituted mercaptans and thiophenols of not too high molecular weight are distinguished by the ready formation of disulphide by the action of ferric chloride or iodine, and in the aliphatic series, by the behaviour towards mercuric chloride solution (see pp. 106, 107).

Sulphonic acids and thio-acids are strongly acidic substances. Thio-acids of the type R·CO·SH react readily with aniline to liberate hydrogen sulphide and to give an acyl anilide. Thio-acids such as thioglycollic acid and thiosalicylic acid are easily oxidised by ferric chloride to the corresponding disulphide. They also react with aldehydes to give crystalline condensation products (see p. 108). The sulphonic acids are stable, and usually readily soluble in water. By reaction with phosphorus pentachloride they are converted into the corresponding chlorides, and can be characterised either as chlorides or as amides.

(b) *Neutral substances.* (*a*) Heat the substance under reflux with 5*N*-sodium hydroxide, and examine the product for alcohols from the esters of sulphonic acids, sulphates, sulphites, etc. The acid should also be identified.

Note.—(1) Phenyl esters of sulphonic acids may also be present, so the solution should be examined for a phenol by saturating with carbon dioxide and extracting with ether.

(2) Although most alkyl sulphates and sulphites are hydrolysed by alkali, di-*n*-propyl sulphate appears to be hydrolysed comparatively slowly.

(*b*) The simple sulphones, sulphoxides, and sulphides are indifferent to alkali. The sulphides are distinguished by the formation of additive compounds with mercuric chloride and with salts of other heavy metals. They also yield sulphoxides and sulphones on oxidation (see pp. 114, 115, 123).

In the absence of sulphides, a portion of the substance is reduced with zinc in acetic acid solution. The formation of a sulphide indicates a sulphoxide. This can be confirmed by oxidation to the sulphone, and in the aliphatic series by the formation of a soluble salt with nitric acid. The sulphones are in general stable to oxidation and reduction.

(f) *Halogen and Sulphur Present, Nitrogen Absent.*

The more common classes of compounds are halogen-substituted sulphonic acids, sulphonyl chlorides and bromides, halogen-substituted thiophenols and sulphides, bisulphite compounds of halogen-substituted aldehydes and ketones, sulphonium halides.

1. When a metal has been found, the substance is examined for the salts of chloro-, bromo-, or iodo-substituted sulphonic acids, and thiophenols, and for bisulphite compounds of halogen-substituted aldehydes and ketones.

2. If the substance contains no metal, it is tested for a sulphonium salt with silver nitrate and moist silver oxide. If this gives no definite result, the substance is classified either as acidic or neutral.

The neutral substances are submitted to alkaline hydrolysis.

Sulphonyl halides give under these conditions the salt of the corresponding acid and the alkali halide. The presence of a sulphonyl halide can be confirmed by the preparation of suitable amides.

In the absence of sulphonyl halide, the product is examined for esters. The examination for sulphides, sulphoxides, and sulphones proceeds as indicated previously.

Note.—The presence of thiophosgene—a red liquid with a suffocating odour and fuming in moist air—will be obvious from the preliminary observations. This can be confirmed by boiling under reflux with water, when it decomposes into hydrogen sulphide, hydrochloric acid, and carbon dioxide. It also reacts with an excess of primary amine to yield a substituted thiourea.

(g) *Sulphur and Nitrogen Present, Halogen Absent.*

The more common types of compounds likely to be met with are sulphates of amines; nitro-, amino-, and azo-sulphonic acids and their salts; sulphon-amides and -anilides; thioamides; nitro- and amino-sulphides and thiophenols; *iso*thiocyanates; hydrazones of sulphonated aldehydes and ketones and derivatives of hydrazine and substituted hydrazine sulphonic acids.

The preliminary observations should afford some indication of the presence of the volatile mustard oils, or of the highly coloured azo-dyestuffs.

1. The substance is treated with cold sodium hydroxide solution. The separation of an amine indicates the presence of a salt, both components of which should be identified and characterised.

If there is no separation of an amine, solubility in dilute alkali of a substance insoluble in water may be due to (*a*) a sulphonamide containing the grouping $-SO_2{\cdot}NH-$, (*b*) thiocarbamides of the type $-NH{\cdot}CS{\cdot}NH-$, (*c*) acids.

Acids should be tested for by their reaction toward sodium carbonate and sodium bicarbonate, and if an acid is found, the nature of the other groupings present should be ascertained.

2. Boil a portion of the substance with aqueous alkali.

Thioamides and sulphonamides derived from aliphatic amines are decomposed more or less slowly with the evolution of the amine or ammonia. This should be confirmed by heating a further amount of the substance with aniline, when the amine is displaced by aniline to give the corresponding anilide.

The product of the action of alkali on the original substance should also be examined for the presence of alcohols and phenols derived from the hydrolysis of esters.

3. A portion of the substance is boiled with dilute hydrochloric acid. Hydrazones and similar compounds are hydrolysed with the regeneration of their components.

4. Heat with mercuric oxide suspended in aqueous alcohol. Thiocarbanilide and similar compounds are desulphurised with the formation of the corresponding carbanilides and mercuric sulphide. Mustard oils give the corresponding urea. If a mustard oil is

suspected, it can be characterised by the formation of a thiocarbamide by reaction with aniline. It should also be hydrolysed by hydrochloric acid to an amine and hydrogen sulphide.

5. If the substance does not decompose bicarbonate solution; does not respond to treatment with mercuric oxide; and is not hydrolysed by aqueous alkali or acid, it is probably a sulphonyl derivative of an aromatic amine. These compounds are hydrolysed by heating in a sealed tube with hydrochloric acid at about 130° or with moderately concentrated sulphuric acid.

Note.—Saccharin behaves as an acid, decomposing sodium bicarbonate solution.

(h) *Nitrogen, Halogen, and Sulphur Present.*

The types of compounds most likely to be encountered are sulphates of halogen-substituted amines; sulphonyl derivatives of halogen-substituted amines; nitrosulphonyl derivatives of chloroamines or halogen-sulphonyl derivatives of amines; nitrosulphonyl halides.

The substance is treated according to the scheme outlined in the previous section.

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